THE American JOURNAL OF Surgery

FEBRUARY 1955

THURSTON SCOTT WELTON, M.D., EDITOR

Symposium on Bronchopulmonary Diseases

Emil A. Naclerio, M.D., *Guest Editor*

SIXTY-FOURTH YEAR OF PUBLICATION

FEBRUARY 1955

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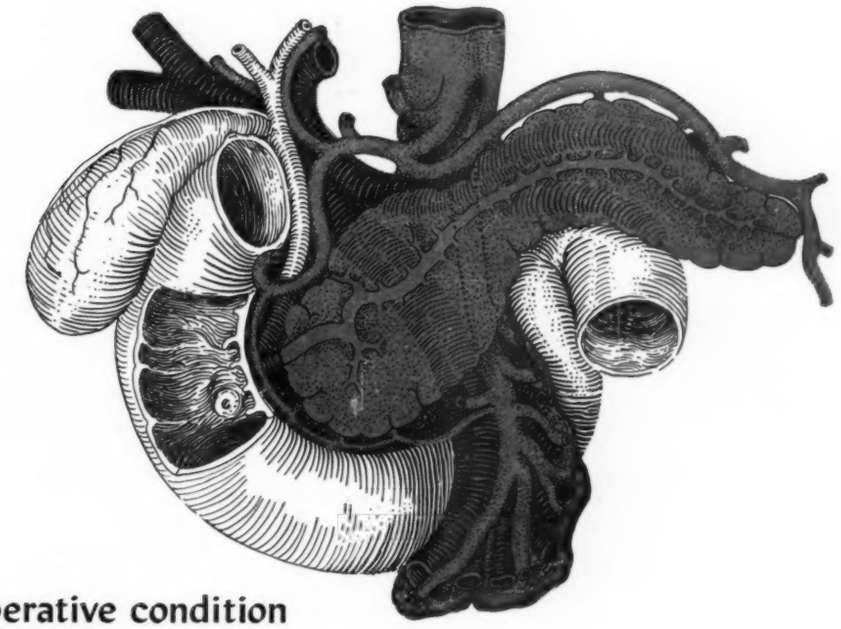

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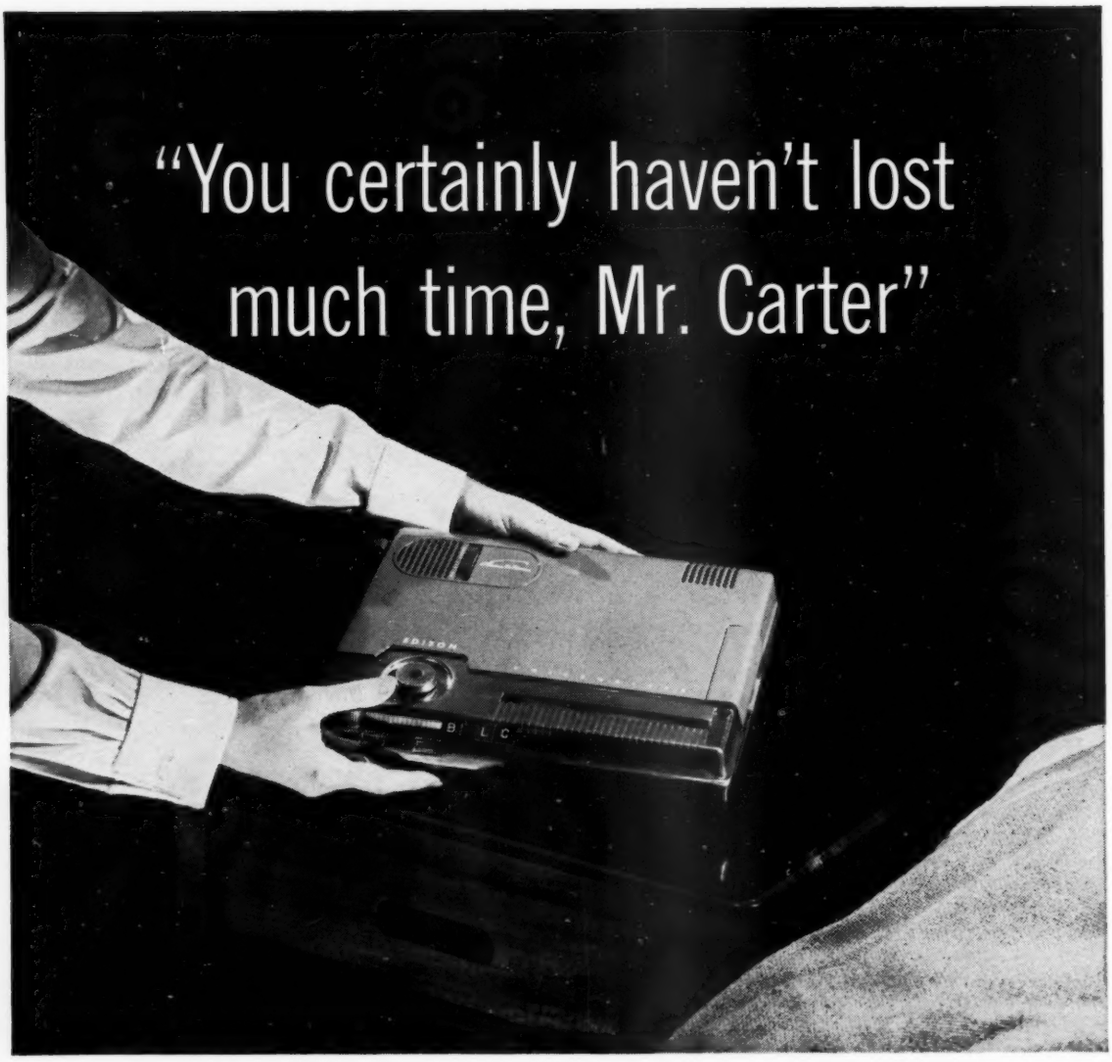

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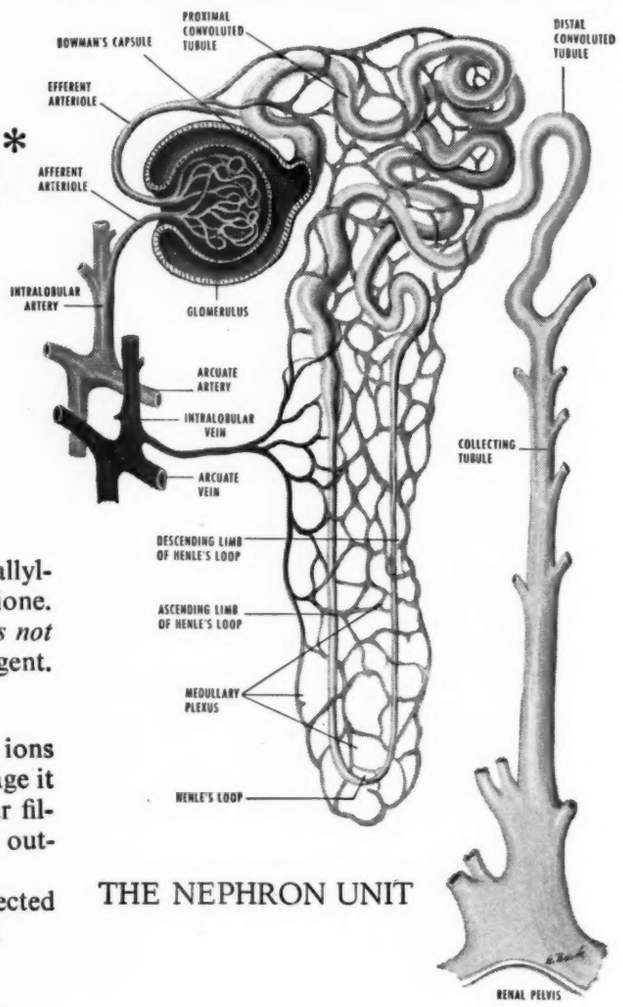

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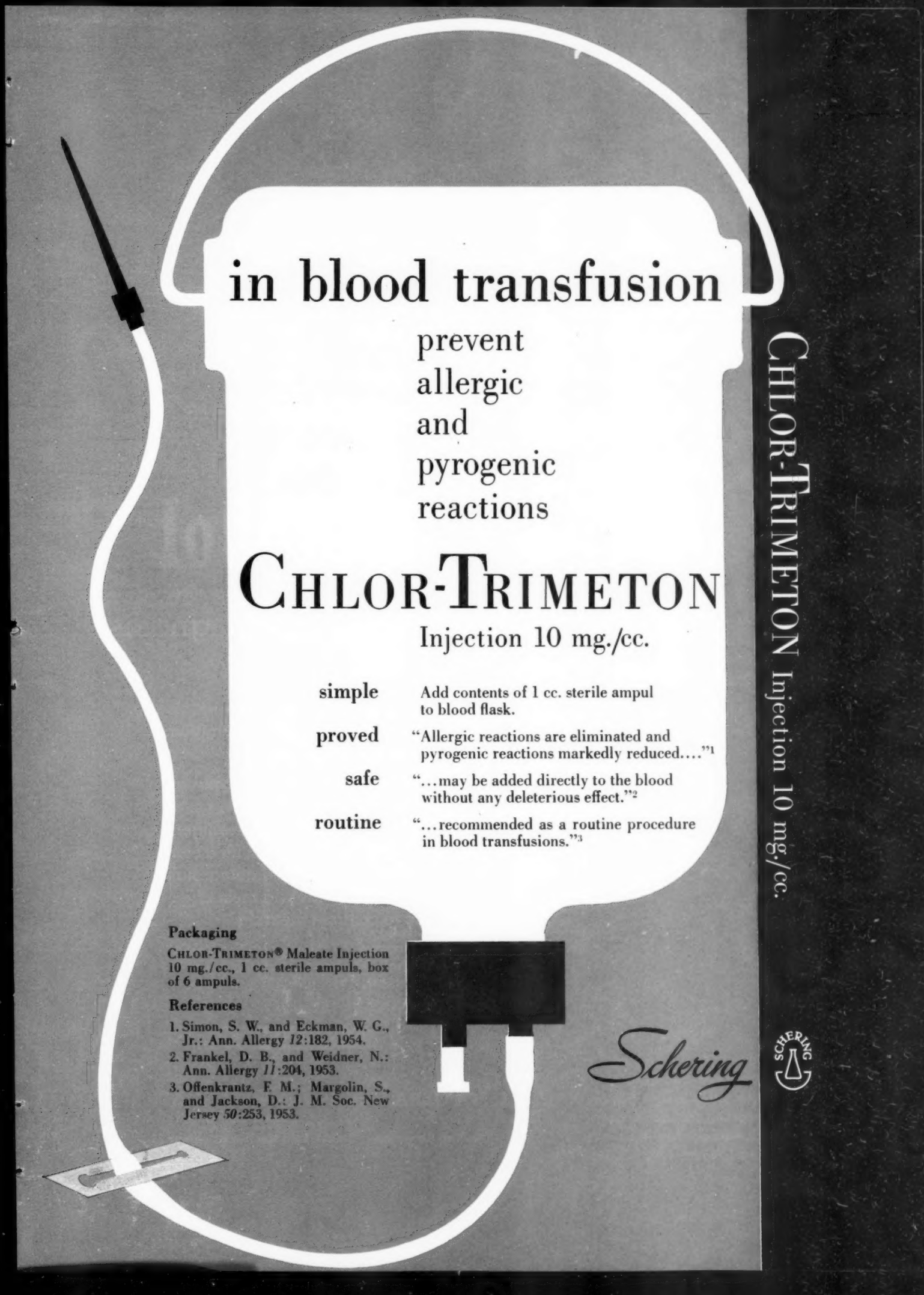
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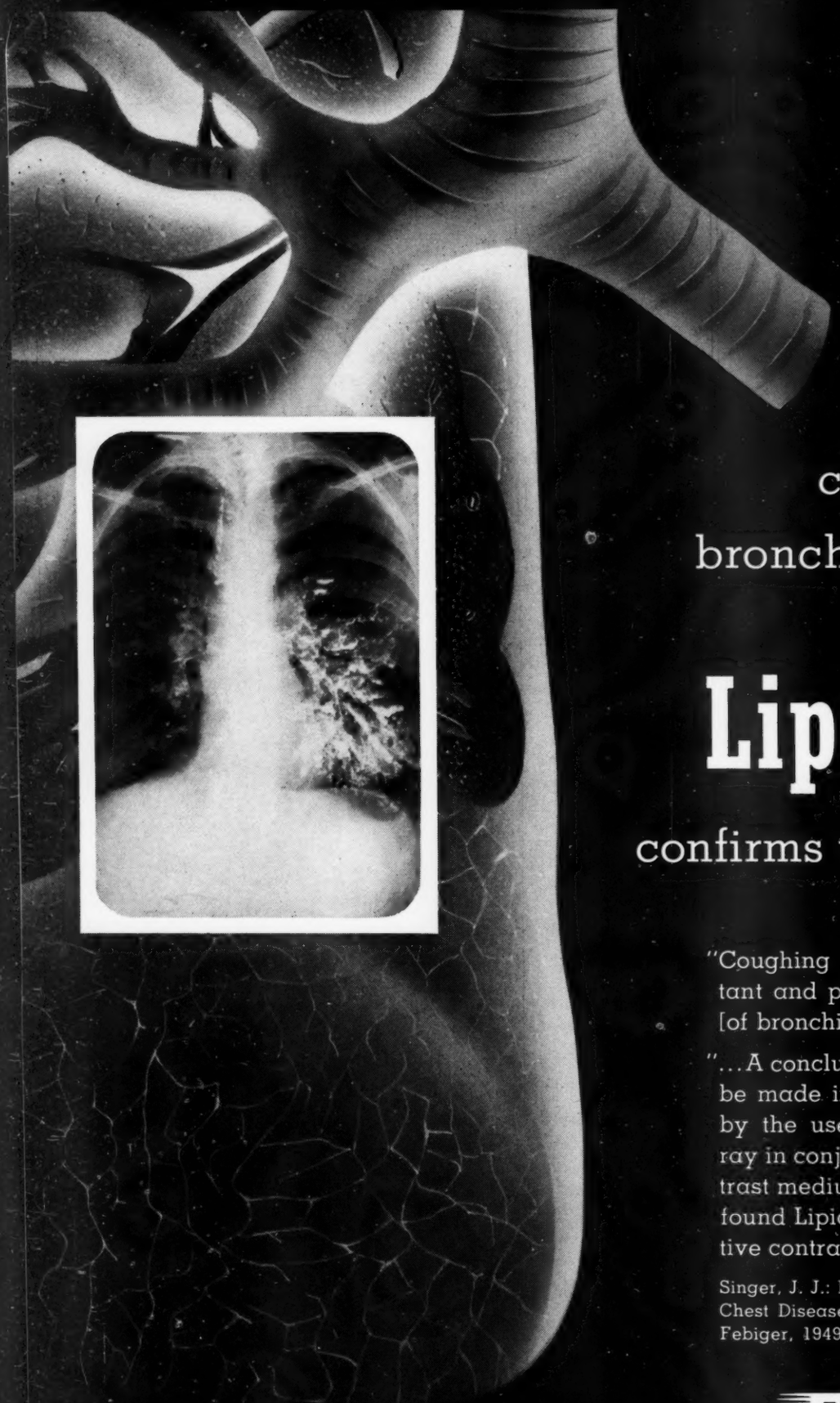

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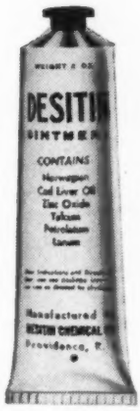

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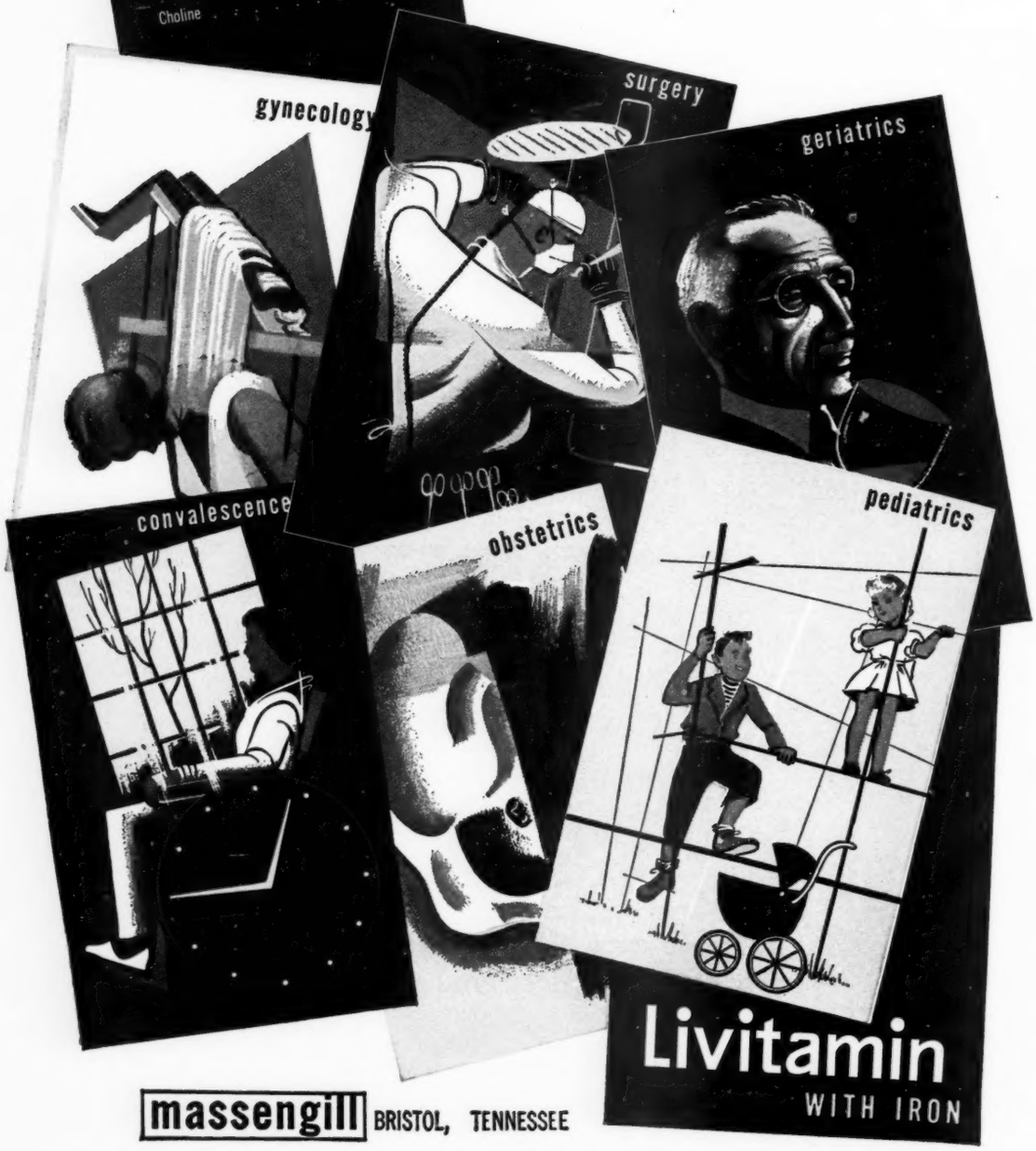

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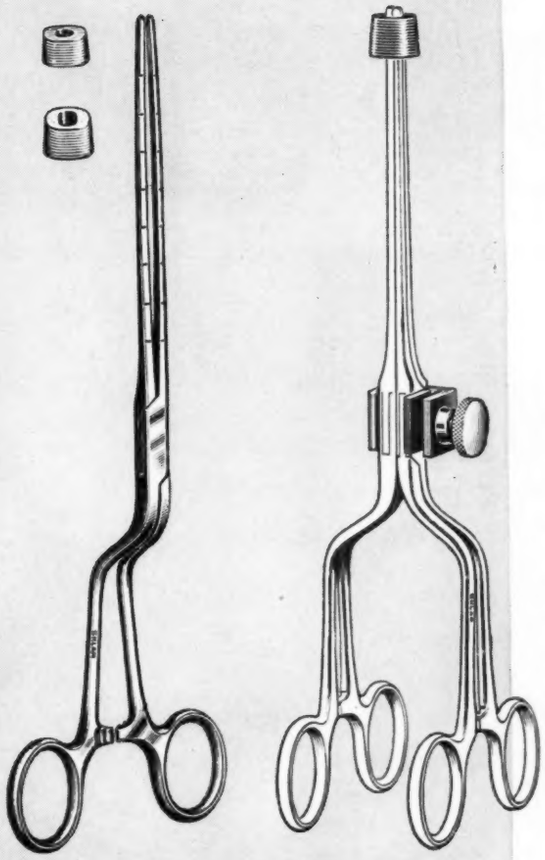

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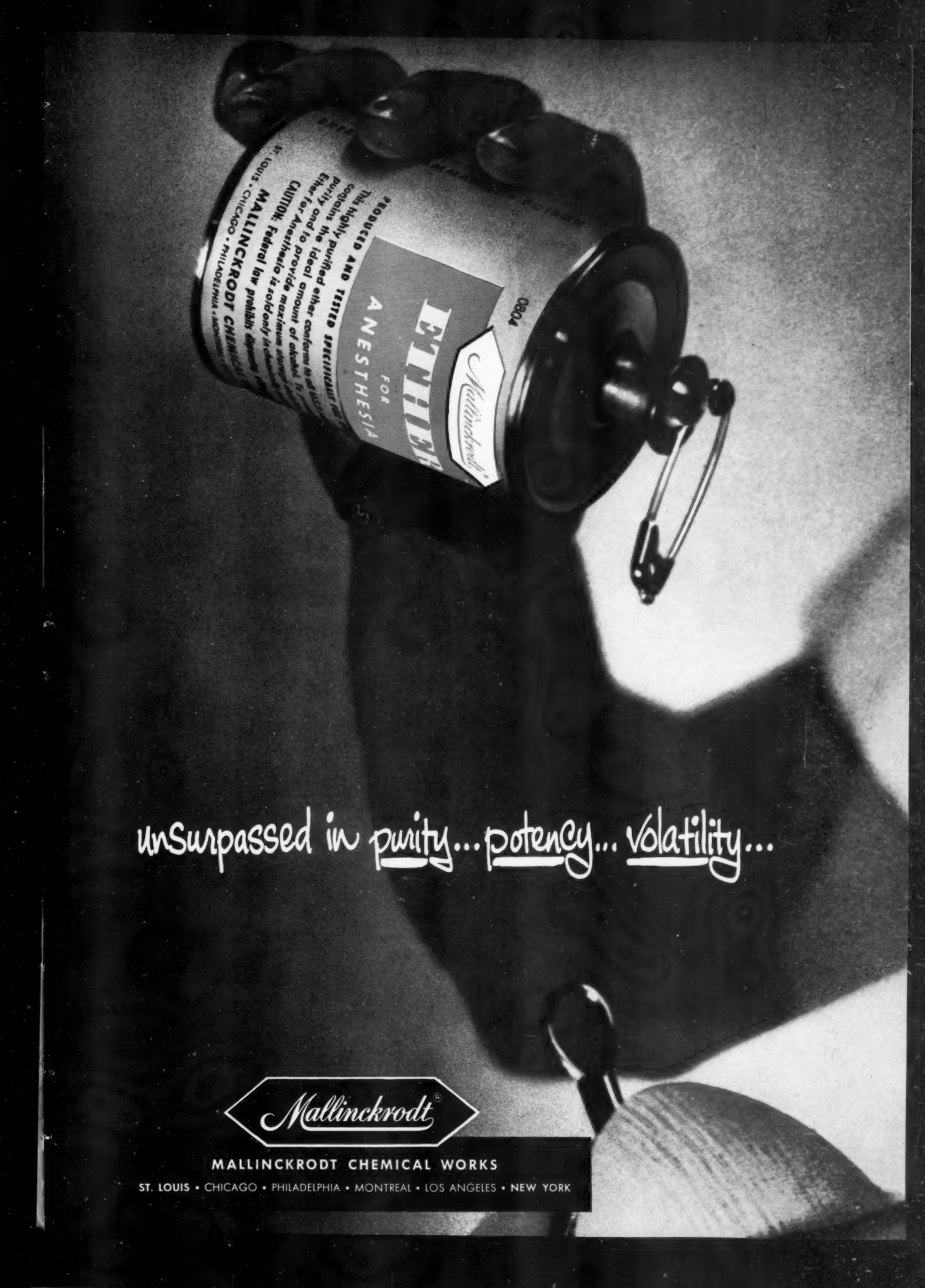
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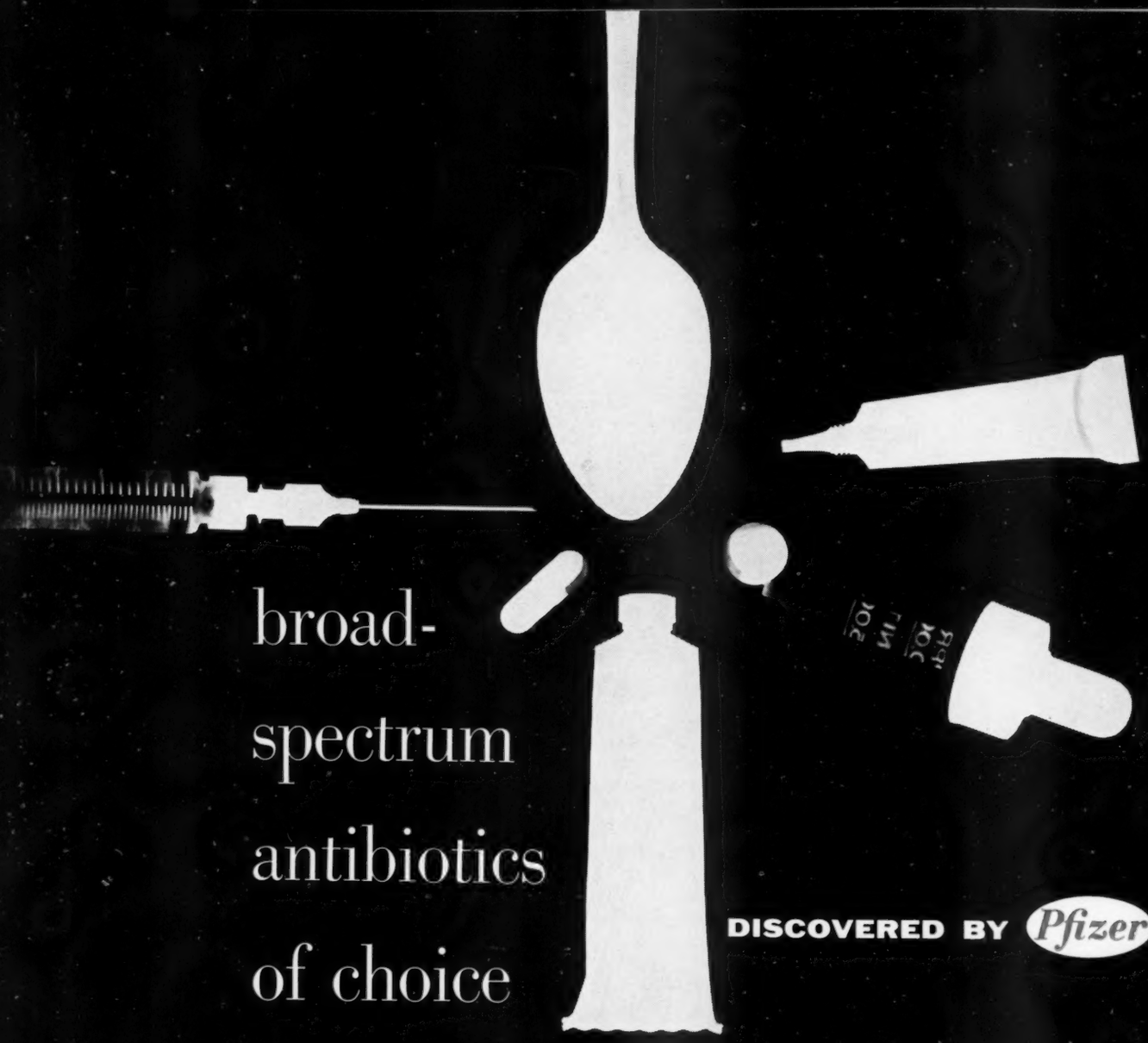

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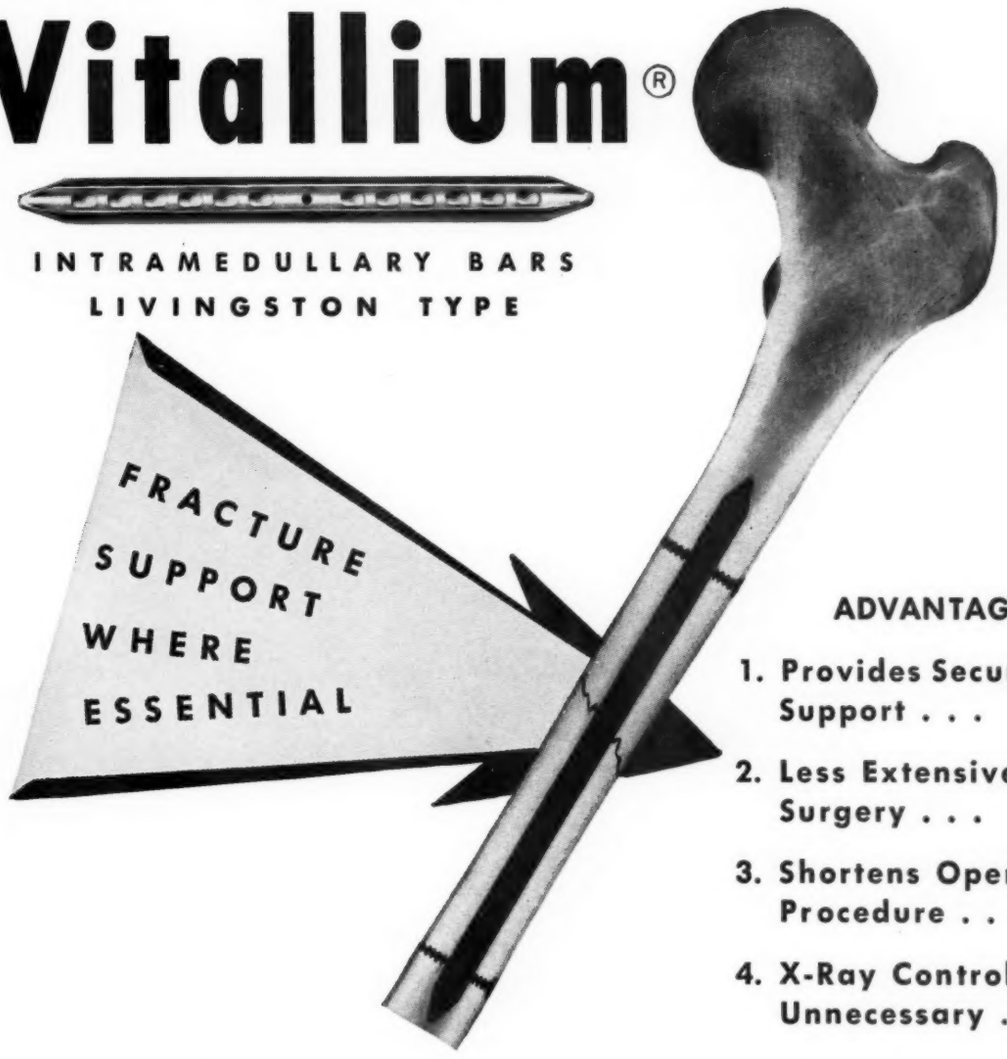

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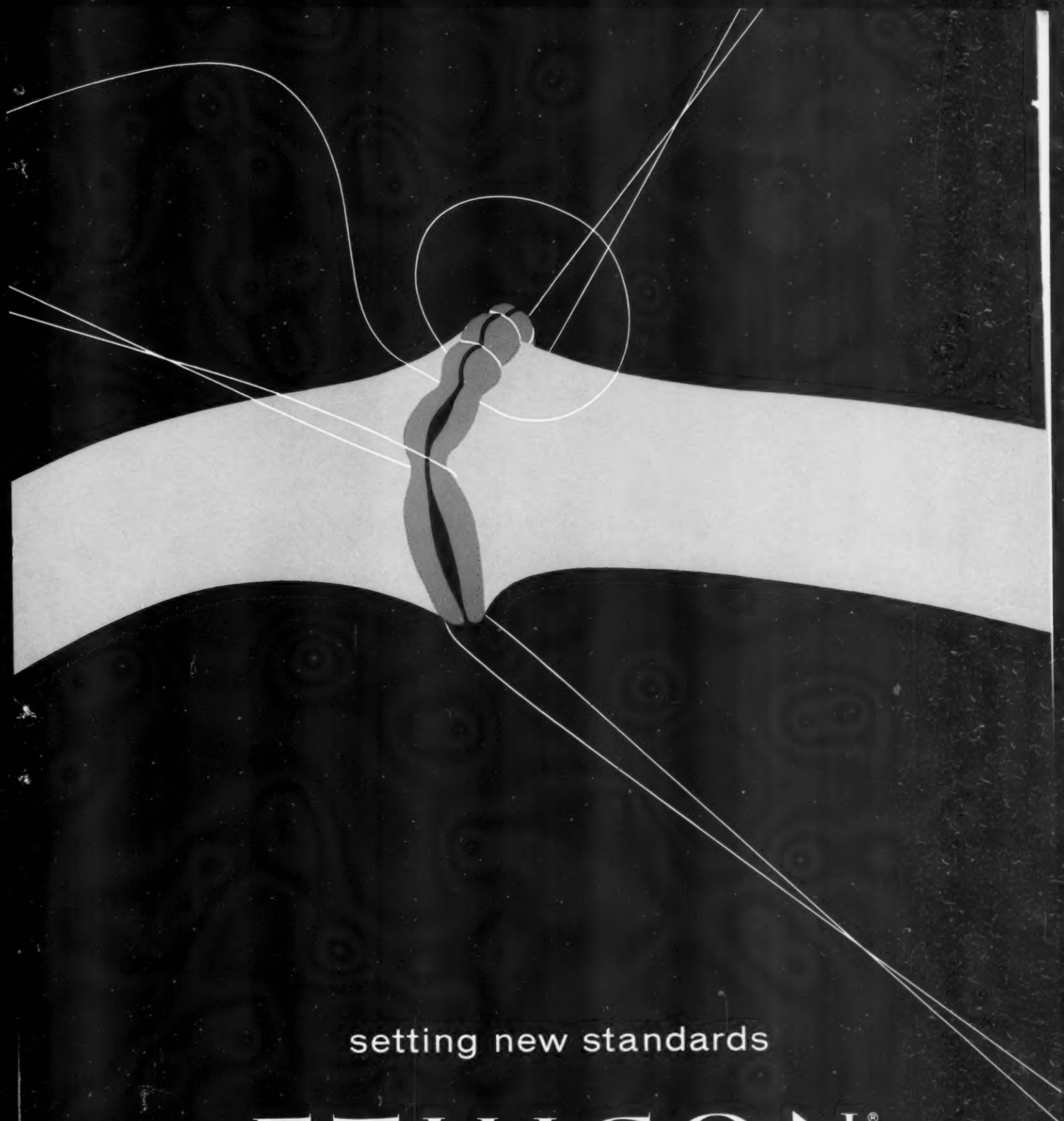

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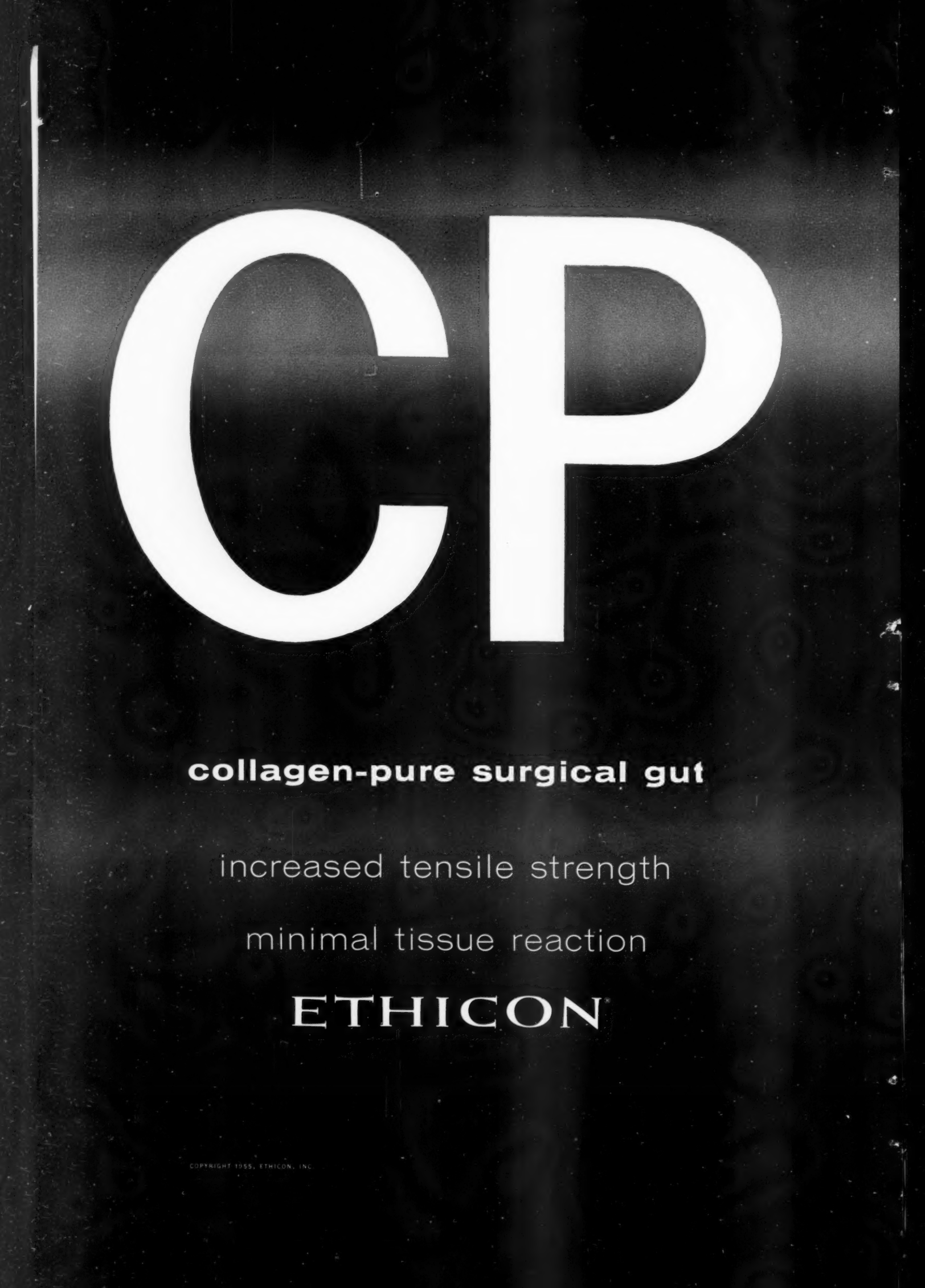

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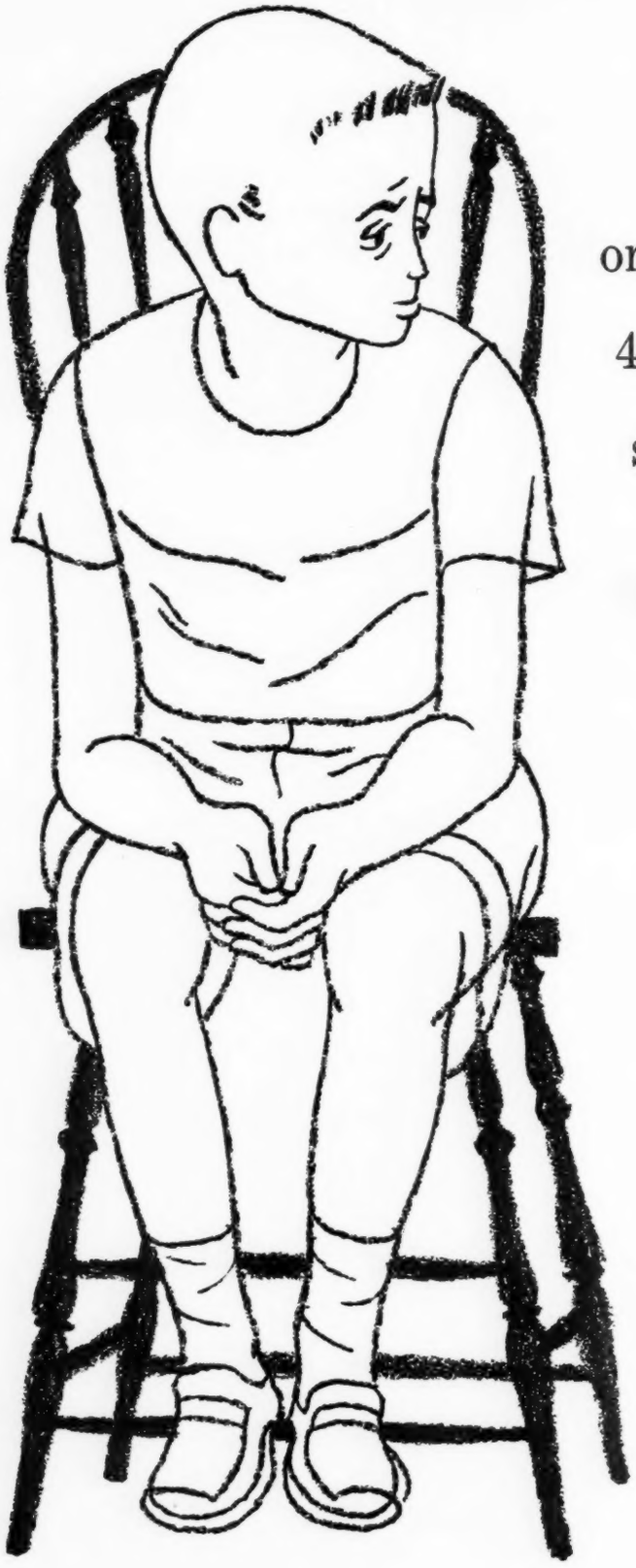

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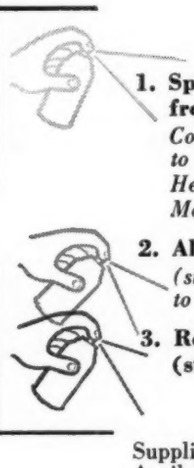

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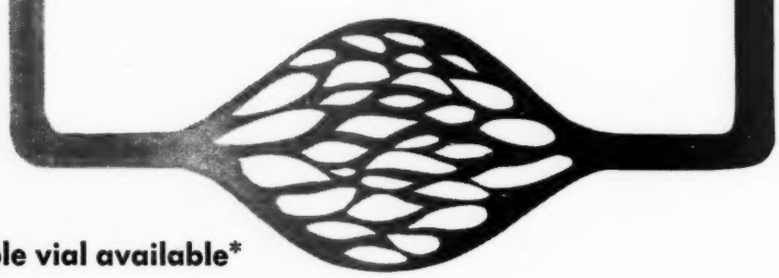

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References: 1. J.A.M.A. 153:1516, 1953. 2. M. Clin. North America 27:189, 1943. 3. Surgery 18:200, 1945. 4. N.N.R. 1954, p. 107.

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BASIC CONSIDERATIONS

Cough, Its Pathology and Management

A. WORTH HOBBY, M.D., *Atlanta, Georgia*

IGNORANCE of the true pathology of the cough mechanism and the confusion in the selection of proper management of this symptom may be due to its constant presence in all degrees of severity. New drugs are accepted slowly because the physician is more familiar with an older product and because the importance of the symptom is minimized. Constant effort is necessary to keep up with the new literature on the subject, as well as a burning desire to learn the cause of each individual cough. The simplest efficient method of management is desirable but not a substitute for a knowledge of the cause and effect. This is even more important when it is realized that 13 per cent of the population of this country will be over sixty-five years of age at the end of this century. Of this 13 per cent, it is estimated that 6 per cent will be "chronic coughers" as a result of many chronic lung diseases. An example is the increase of hypertrophic emphysema, or consider the coughing in bronchiectasis which "is the second commonest lung disease. The National Health Survey of 1935–1936 showed 1,700,000 persons to be affected by chronic bronchitis. To these cases many of the 1,150,000 persons with chronic sinusitis can be added, since chronic bronchitis and sinusitis frequently complicate each other. Furthermore, most cases of chronic asthma, although still indexed among the 3,500,000 victims of hay fever and asthma, represent the nonallergic infectious type of asthma rather than true allergy. This survey would then indicate that in this country alone, at least 2 to 3 million persons suffer from chronic bronchopulmonary disease."[1]

PATHOLOGY

Full credit should be given to Banyai,[2–6] the pioneer in bringing to our attention the pathology of the cough mechanism.

The basic pathology of the cough mechanism changes only with addition of new knowledge of the nerve pathways. All classifications of cough are unsatisfactory because they are as numerous as there are descriptive adjectives and lead only to confused thinking. Therefore, for simplicity of understanding, the author has listed the following causes of harmful cough[7]: (1) stimulation of the cough reflex by extrapulmonary irritation due to drainage from the paranasal sinuses, an elongated uvula, and pressure on the trachea or bronchi by medi-

astinal inflammation, tumors or dilated blood vessels; (2) non-inflammatory lesions of the bronchial tree such as benign or malignant tumors; (3) inflammatory processes of the bronchi or the lung parenchyma without the formation of exudate but with constant irritation of the cough center, as in the dry cough of early acute bronchitis; (4) mucopurulent or mucoid secretions resulting from inflammation of the bronchial tree that are too tenacious to be removed by cough, as in the paroxysmal stage of whooping cough; (5) transudation in the alveoli during heart failure; (6) obstruction of the bronchial tree due to pathologic changes which cause retention of the secretions and exudates distal to the obstruction (7) atelectasis because the definition of cough cannot be fulfilled; (8) emphysema as result of weakening and destruction of the elastic structures, reduction of the intrapleural subatmospheric pressure, abnormally low position of the diaphragm; (9) fatigue and exhaustion of the expiratory muscles, as in fibrotic tuberculosis and pulmonary fibrosis; (10) psychogenic cough such as that produced by the exhibitionist; (11) allergies.

Cough is defined as a sudden violent expulsion of air after deep inspiration and closure of the glottis. The helpful cough has as its purpose the removal of abnormal mucus, inflammatory products, foreign bodies, products resulting from circulatory congestion and all irritating sensations in the respiratory tree. To be successful a cough must produce effective drainage of the lung without undue stress on the tissues of the body.

During cough, particles are propelled through the air at the rate of 150 to 160 feet per second. In normal-toned conversation these same particles are sprayed for a distance of 8 feet. A cough sprays about 12 to 15 feet and a sneeze sprays as much as 20 feet.

Further pathologic knowledge is necessary to appreciate the full significance of the previously outlined causes of cough. The cough center located in the medulla is near the sensory portion of the vagus nerve and also near the vomiting center. Peripheral and central stimuli act on the cough center. Coughing is also produced by stimulation of the sensory endings of the glossopharyngeal and vagus nerves.

Eight groups of branches of the vagus nerve are associated with cough. They are described as: Arnold's branch to the ear which is stimulated by wax, eczema, etc., causing a cough; the pharyngeal branch; the superior laryngeal branch sensory to the base of the tongue and larynx, frequently a cause of coughing. Among this group is also found the inferior laryngeal branch (motor), which may produce an inefficient cough; and cardiac branches, which are indirect causes through circulatory failure. The last three in this group are listed as: the pulmonary branches which are concerned in the cough of gross pulmonary or pleural diseases; the gastric branches which occasionally cause coughing due to dyspepsia; and the esophageal and precardial branches.

Tussal insufficiency is most often seen in myasthenia gravis, bronchial asthma, pulmonary emphysema, bronchiectasis, lung abscess, blocked tuberculous cavities and atelectasis. Tussal insufficiency plus severe cough increases the rate of metabolism and prevents rest. Other results are pulmonary hemorrhage, vomiting, spontaneous pneumothorax, headache, loss of weight, exhaustion, loss of appetite, elevated temperature, insomnia, marked dyspnea, cyanosis, thoracic pain, fractured ribs, mediastinal emphysema, subcutaneous emphysema, urinary incontinence and, indirectly, myocardial failure.

Advanced mitral stenosis may cause the pulmonary vascular pressure to rise producing pulmonary congestion which in turn produces a cough and blood streaked sputum. Add to this a slight infection and complications multiply.

A discussion of the pathology of cough would be incomplete without a consideration of "tussive syncope."[8] Circulatory disturbances due to coughing, rather than epilepsy of the larynx, is believed to be the cause of the phenomenon. Pressures in the right ventricle during coughing have been proved to be abnormally high. Convulsions may be present. There is a congestion of the cerebral veins, decreased cardiac output and anoxemia, all of which may cause syncope in some cases.

MANAGEMENT

Even though city dwellers and smokers all have morning coughs, they should not be allowed to go unobserved or untreated when persistent. An adequate history embraces all aspects of the condition and must be accompanied by complete physical examination with

all laboratory studies necessary for diagnostic purposes.

Surgical Intervention. When tumor, foreign body, elongated uvula, dilated blood vessels and atelectasis are found to be the cause, appropriate surgery is most often indicated. Surgery is needed often in infections such as bronchiectasis, lung abscess, empyema and other pulmonary complications. Deep x-ray therapy and/or nitrogen mustard may or may not be indicated—alone or in conjunction with surgery in the foregoing conditions. The presence of infection, the type of infection, the location, extent and character of the lesion will indicate the treatment. It goes without saying that the cure of the disease stops the cough.

Physiotherapy postoperatively in thoracic surgery is a must. It is also useful in chest abnormalities, faulty drainage of the respiratory tree, faulty respiratory movements, bad habits and chronic lung infections.

Postoperative Atelectasis and Pneumonia. Methods of preventing postoperative atelectasis and pneumonia are important to the surgeon. Greene[10] states that postoperative "Atelectasis and pneumonia are preventable by a strict regimen of detecting the abnormal tracheo-bronchial tree in the predisposed patient and removing potentially obstructing material by vigorous coughing induced during the early postoperative period. The appearance of the atelectasis within forty-eight hours after an abdominal operation can—except for rare occasions—be regarded as an evidence of imperfect anesthetic care." Prophylaxis depends on utilizing the induced cough, produced by deep breathing followed by a vigorous tussive squeeze and forceful bechic blast. Deep breathing may be induced by carbon dioxide, intravenous nikethamide, back slapping, side-to-side rolling of patient, topical anesthesia of the larynx, sudden inhalation of ether, endotracheal catheter suction, prolonged postoperative wound analgesia, intravenous procaine, early ambulation and intravenous administration of sodium iodide. All depends on the ability and cooperation of the patient to cough vigorously.

The so-called "wet" cough is always to be regarded with suspicion by the surgeon. The most common cause for this type of cough is the inhaled smoke of twenty cigarettes per day, and the next most common cause is infection. Asthma, marked obesity, emphysema or thoracic kyphoscoliosis are also associated with a wet cough. However, this wet cough may fail to develop because of severe painful surgical disease, debility, stupor, excessive premedication, extreme obesity, abdominal distention or emphysema.

The increasing number of emphysematous patients demands an intimate knowledge of the anatomic and physiologic mechanism of the terminal respiratory system. All emphysematous patients cannot be correctly placed in one type of emphysema. The cough of each is manifestly different to those experienced in that work. Rhythmic relaxation and contraction of smooth muscles in the walls of the bronchioles is a normal process. Spasm of these muscles causes occlusion of the smaller bronchioles. This may result from irritants or allergies as foreign bodies and gases. The bronchioles direct their peristaltic motion from the smaller to the larger structures. With this in mind, it is easy to see that emphysema (genuine) is due to: (1) increased intrapulmonary pressure due to strenuous coughing; (2) infections and other pathologic changes which result in extensive degenerative alterations in elastic elements of the lung; (3) partial bronchial occlusion of the check valve type.

Cough is one of the predominant features of the common cold and is mentioned here because of the economic bearing on industry. Statistics[11] state that this condition accounts for the loss of 100 million work days, or in excess of one billion dollars each year in the United States. There is an average of two and a half colds for every man, woman and child in the United States each year. These figures were compiled before the common use of "air conditioning," which has probably increased common colds by 15 per cent. The author has noted that although "air conditioning" may cleanse and cool the air, the "coughers" are much worse because of the increased postnasal drainage. This is caused by rapid change in atmospheric conditions while at work or at home and the "outside natural air." The mucous membranes of the upper respiratory tract cannot become acclimated with the same rapidity. Add to this the insult of tobacco smoke (regardless of whether inhaled or not) and varying pathologic changes of the mucous membrane are sure to follow. The length of exposure, virulence of the bacteria, amount of

bacterial exposure, acuteness of the atmospheric changes, and lack of resistance of the host must contribute to the type of disease to follow.

Ordinary hilar adenopathy in childhood tuberculosis produced no cough but large caseous nodes may cause pressure on bronchi or rupture into bronchi producing cough. In cases of persistent coughs, colds and frequent respiratory episodes in those who fail to gain weight, fibrocystic disease of the pancreas should be suspected.

The etiology of cough is more often found in the upper respiratory tract in children than in adults. Large adenoids, excessive lymph tissue in the pharynx and excessive carbohydrate diet[12] all cause excessive secretion and produce cough in addition to the usual infectious processes.

The treatment of cough in children and adults differs in the child's ability to receive adult methods. Ice collars, painting of the throat, packs on chest and unpalatable mixtures are to be avoided.

DRUG THERAPY

There is much disagreement in the choice of cough remedies. "It seems to be a field in which poly-pharmacy and shotgun mixtures have enjoyed immunity from attack, for it makes little difference what the ingredients are or how many are included if the mixture only expressed the art of mixing palatable materials. . . . It is well to confine the term cough remedy in a specific sense to a drug which acts to raise the threshold of the cough center in the central nervous system, or acts peripherally in the respiratory tract to reduce the impulses which pass to the center, or a mixture that combines both actions."[13]

Proper management of cough necessitates the application of knowledge of many methods. It is surprising to note that some authors still deny the proved action of certain drugs. More than 125 articles published since 1949 have been reviewed and the need for clarification and a unanimity of thinking is more and more evident. New drugs which have been proved more efficient than the old should be accepted and used. Definitions should be changed to express new knowledge. As an example, the term "expectorants" is obsolete as applied to cough remedies and obscures clear thinking. An outstanding textbook lists and defined expectorants as drugs which assist in the removal of exudate from the respiratory tree, classifying them as sedative, stimulant and anodyne—the latter referring to opiates which depress the cough mechanism by central action. The term expectorant should be confined to peripherally acting cough remedies; usually irritants which act on the mucous membrane directly or reflexly to increase secretion. The increase is apt to make the secretion more alkaline and the raise in pH renders the mucus thinner and less viscid. It protects a dry mucous membrane. Intimate knowledge of the action of each drug or combination of drugs will insure the best results, but the drugs must be selected on the basis of pulmonary finding and the general condition present. Even the most efficient management of cough does not relieve the physician of the responsibility of treating the underlying disease on an etiologic basis.

Morphine. Morphine and its alkaloids depress the irritative reflex and decrease the amount of bronchial secretions. If used they should be confined to the dry, hacking cough and never used in a wet cough. Although morphine is one of the oldest and most commonly used drugs, it should be very rarely used. Morphine should never be used in a case of hemoptysis. It reduces bleeding by sedation and slowing the circulation, but suppresses the elimination of blood and clots. If tuberculosis is present, spread of the disease is encouraged. It should be known that this drug and even codeine: (1) depresses the respiratory center, (2) diminishes the tone of striated muscles involved in respiration (the muscles of the diaphragm are responsible for 37 to 47 per cent of the ventilatory function of the lungs and in a large measure for the normal cough mechanism),[5] (3) inhibits glandular action of the bronchial mucous membrane, (4) causes spasm of the smooth muscles of the bronchi and bronchioles, and (5) causes paralysis of bronchial peristalsis.

The only excuses for the use of morphine are: (1) inoperable lung and mediastinal tumors associated with uncontrollable pain, (2) aortic aneurysm causing pressure that cannot be controlled otherwise and (3) certain cases of cardiac decompensation with cough. (4) Lansdown[13] believes that old debilitated patients in a terminal illness such as bronchi-

ectasis should have morphine or codeine, even if it shortens their life, if it affords them comfort.

Dibydrocodeinone. A codeine derivative called hycodan bitartrate® and para hycodan® are far superior in every way to codeine. Depression, constipation, nausea and the habit-forming ability are far less. It is an effective and satisfactory antitussive agent which relieves cough without interference with expectoration.

Caramiphen ethanedisulfonate (bis-[1-(arbo-B-diethylaminoetroxy)-1-henylcyclopenane]), an anticholinergic compound,[14,15] was found to have excellent antitussive effect in the dry or moist unproductive cough and is manufactured under the name toryn® (Smith, Kline & French Laboratories). Romilar hydrobromide® (Hoffmann-La Roche Inc.) is found to be less depressing and less habit-forming than codeine and its derivatives and is essentially free of atropine-like effects.[16]

Dextromethorphan hydrobromide (dextro-3-methoxy-N-methylmorphinan), 4 mg., was compared[17–19] with codeine sulfate, 17 mg., and a placebo medication. The antitussive effectiveness of the first was equal to that of codeine, but the side effects (nausea, constipation, etc.) were the same as that of the placebo medication.

Methadone[20] is similar to morphine but more powerful. It does not increase the rate of production of respiratory tract fluid. Other names for this product are dolophine,® madone, physeptone and amidone. It is habit-forming.

Bronchocatharsis[5] is accomplished by so-called expectorants not only by facilitating expectoration but also by accelerating resorption of inflammatory exudate. The latter process is carried out by digestion or dilution and liquefaction through the admixture of the secretions of the glands of the bronchial mucosa and the alveoli.[21] Dehydration will prevent any expectorant from producing the proper results.

Potassium Iodide. Heading this list should be potassium iodide with the emphasis placed on the size of the dose. The authors of two monographs on cough have stated that there is no evidence that this drug will increase the respiratory tract secretions. This statement is in error as proved by direct visual observations of the respiratory tree through the bronchoscope before, during and after the oral administration of potassium iodide. Hopkins[22] observed a dry bronchi become "wet" enough to aspirate the secretions fifteen to twenty minutes after the oral administration. Herxheimer and McAllen[23] used potassium iodide intermittently in doses of 15 to 25 gr. and produced a real increase in respiratory secretions. Many other authors also confirm the value of this drug, but the literature fails to show that these benefits are obtained only when large doses are used. The author finds that the dosage should start with 10 drops of a saturated solution, three times a day in water after meals, increasing one drop each day up to 30 drops, three times a day. Beneficial results usually begin when the patient has reached 20 drops after each meal. Iodine reactions are common and must be controlled promptly by omitting or reducing the dose. The pH is lowered in the bronchi where the secretions present are diluted and made thinner and less viscid.

Potassium iodide is not contraindicated in pulmonary tuberculosis as has been stated by some authors. The thinning out of the secretions produces more sputum and floats out bacteria already present, but it does not cause reactivation or spread of the disease.

Ammonium Chloride. The next most widely used expectorant is ammonium chloride. Ammonium carbonate is better but must be dissolved in alcohol before adding to a vehicle. This detail appears to be little known and for this reason it is rarely used. This drug increases the respiratory tract fluid by reflex action on the stomach. When the gastric branches of the vagus are cut, no action results. Here again large doses must be used.

Cass[24] compared terpin hydrate, ammonium chloride and aromatic syrup with glyceryl guaiacolate. The latter contains 100 mg. glyceryl guaiacolate, 1 mg. dioxyephedrine hydrochloride in each 5 cc. of aromatic syrup and is known as robitussin® (Robins Company, Inc.). He states that robitussin used in tuberculosis patients was markedly superior to the others, causing marked increase in the respiratory tract secretions without increasing the volume of sputum.

Combinations of drugs in suitable vehicles are numerous and space does not permit a detailed description. However, the trade names and manufacturers of a few are given with a very brief comment: (1) autosen® (E. R. Squibb & Sons) containing prophenyridamine

maleate, codeine phosphate and alcohol, for non-expectorant cough sedation; (2) extosen® (E. R. Squibb & Sons) containing propheny-ridamine maleate, ammonium chloride and ephedrine sulfate, for asthmatic cough with thick mucus; (3) cosanyl® (Parke, Davis & Company) containing eight ingredients, the principle one being dihydrocodeinone bitartrate, used in dry, painful coughs; (4) benylin® (Parke Davis & Company) containing six ingredients, the principle of which is benadryl hydrochloride and ammonium chloride, for allergic cough where the sputum is very thick and in emphysematous patients;[16] (5) methajade® (Sharp & Dohme) containing five ingredients, the principle of which is methadone hydrochloride and an antispasmodic, used primarily in exhausting paroxysmal coughs; (6) coricidin syrup® (Schering Corporation) contains dihydrocodeinone bitartrate, chlortrimeton maleate, sodium salicylate, sodium citrate, caffeine and glyceryl guaiacolate, and is combined in a palatable syrup acceptable to all ages; (7) theophylline ethylenediamine plus diphenhydramine hydrochloride (hydrillin compound®) (G. D. Searle & Company) combines aminophylline with benadryl and is a most effective antihistaminic antitussive.

Nauseant expectorants such as ipecac, emetine, tartar emetic, apomorphine and drugs acting through the saponins (as squill, senaga and grindelia) are supposed to increase the secretions and lessen the viscosity of the bronchial mucus. However, except for ipecac in pediatrics, the entire group can be forgotten. Ipecac will relax the smooth muscles in the bronchi but will not lower the pH.

Demulcent expectorants such as syrup of acacia, licorice, glycerin, cane sugar, "cough drops," hot drinks are described at length in the English literature but are rarely prescribed in the United States. These are primarily used by those who do not believe that the saline expectorants will increase the bronchial tree fluid. Mildly irritating expectorants as creosotes (calcium creosote and creosote carbonate), guaiacol (potassium sulfonate in syrup), terpin hydrate, balsams of Tolu and Peru, tar and terpin are supposed to diminish bronchial secretions. The first, creosote, is the only one worthy of mention. This drug, given after meals in the form of calcreose® compound, is very efficient in bronchiectasis, bronchial asthma and emphysema. It may well be said that if the other drugs "cure" the patient, he did not need a cough remedy in the first place except for psychologic reasons. Never forget that some coughs should not be stopped and that some will stop in a reasonable period without treatment. Occasionally a simple upper respiratory infection may cause a cough that is the predominant symptom. Through severe blasts and long volleys the cough may produce sufficient irritation to sustain itself through a chain reaction long after the primary condition is gone. This kind of cough is quickly cured by this type of expectorant.

Antispasmodic drugs such as atropine, belladonna, stramonium, lobelia, hycocyamus, epinephrine, ephedrine, nicotine and papaverine find a limited use. The causative organisms of a common cold multiply best in a wet media. The addition of atropine or belladonna to other supportive medication will greatly shorten the course of a common cold and add much to the relief of the patient.

Coughing and dyspnea of emphysema may be greatly benefited by the use of small doses of ephedrine sulfate when combined with effective doses of aminophylline. Orthoxine® (methoxyphenamine hydrochloride) (Upjohn Company) has less side effect and is about as effective as ephedrine. The effectiveness of aminophylline is enhanced by the addition of anti-nausea agents as in dainite® (Irwin, Neisler & Company) and cardalin® (Irwin, Neisler & Company).

Strychnine, coramine® and cordiazol are said to promote expectoration but are rarely used.

Gases. Carbon dioxide aids in increasing the respiratory motion and, in turn, the removal of inflammatory products from the bronchi. It is to be noted that shallow breathing found in debilitated patients, as an effect of general anesthesia, in depression of the respiratory center by narcotics or in anoxemia is harmful.

Banyai[5] states that carbon dioxide benefits by: (1) preventing exhaustive spells of coughing which gives more rest, (2) converting an unsuccessful cough into a successful cough, (3) increasing the amount of sputum which is made thinner, more serous and watery, and (4) reducing the need for other drugs and narcotics. Its effectiveness is due to: (1) stimulation of all muscles involved in breathing, (2) stimulation of myoclastic structures of the

lung, leading to vigorous peristaltic movements, and (3) its liquefying qualities.

Short inhalations of 5 to 10 per cent carbon dioxide with oxygen are most useful in increasing the rate of respiration and the volume of air in the lungs, in augmenting the auricular output of the heart, in raising the diastolic and systolic blood pressures, and in increasing the pulse rate and pulse pressure. Contraindications for the use of carbon dioxide are: (1) recent pulmonary hemorrhage, (2) marked emphysema, (3) widespread pulmonary fibrosis without atelectasis, bronchiectasis or mucopurulent retention in the air passages, (4) acute plastic pleurisy, (5) pleurisy with effusion, (6) hypertension and (7) coughs with source extrapulmonary in origin.

Much has been said in this paper about the association of the bronchial secretions or fluid with cough. The relatively new work of Arnold, Carbasi,[25] Segal and others[16,26] must be included in this discussion. These authors refer frequently to the work of Barack, Beck and others in offering a new approach to removal of obstructive secretions from the bronchial tree with the use of oxygen under positive and negative pressure. The procedure is not complicated but requires study and selectivity of patients. When combined with bronchodilator aerosols in asthma and chronic pulmonary emphysema, the results are gratifying. The explosive passage of air out of the lungs brings with it sputum and secretions otherwise unexpelled. Further use of the Eliot exsufflator with bronchodilator aerosols in chronic lung diseases is recommended in selected cases.

Aerosol. Antibiotics in aerosol therapy are used less and less, having proved to be disappointing in results. Antibiotics are efficient when given intramuscularly if the exudate, mucus and secretions in the bronchial tree are liquefied. The object of the aerosol should be to liquefy the bronchial content and to shrink the mucous membrane of the entire respiratory system. This promotes drainage and cleansing and better results from all medication. The objections to antibiotics by aerosol are: (1) They are not effective if the mucus and exudate are thick and purulent, and antibiotics are not given intramuscularly or orally at the same time. (2) They produce objectionable local reaction (increasing numbers of patients return after the second or third antibiotic aerosol treatment with an increased cough, red and swollen mucous membrane and general discomfort). (3) The procedure cannot be carried out often enough to give its best results unless the patient is hospitalized. Equally good results can be obtained from the use of oral or intramuscular antibiotics and a liquefying aerosol given once a day.

Such a liquefying aerosol is exyethylated tertiary octylphenolformaldehyde polymer 0.125 per cent, in combination with sodium bicarbonate 2 per cent and glycerin 5 per cent (alevaire®, Winthrop-Stearns, Inc.). It is combined with epinephrine 1:1000 by the author. This combination has been found most effective in liquefying the mucus by lowering surface tension, creating an alkaline media and shrinking the thickened mucous membrane. Allergic manifestations seem to respond about as well as infections. Antibiotic therapy given intramuscularly should always be used in the presence of infection.

Varying combinations of the sympathomimetic drugs are acclaimed by various authors. Racemic epinephrine hydrochloride (vaponefrin,® Vaponefrin Company) or isopropylartenol hydrochloride (isuprel,® Winthrop-Stearns Company) appear to be efficient relaxors of bronchospasm. One author[16] finds 0.5 cc. of 2.25 per cent isuprel, 0.5 cc. of 1 per cent phenylephrine hydrochloride (neosynephrine, Winthrop-Stearns, Inc.) a bronchovasoconstrictor, and 0.5 cc. of an aqueous solution containing 0.125 per cent of alevaire to be of excellent value in relieving cough in emphysema.

For the sake of completeness, the use of pancreatic desoxyribonuclease is mentioned in control of cough in the presence of bronchial infection, bronchiectasis or tenacious purulent secretions.[16] This enzyme, called pancreatic dornase, is used as an aerosol in addition to other measures such as pneumoperitoneum, antimicrobial therapy and humidification.

Instillations of oil, iodinized oil and oil combined with the sulfonamides or the antibiotics may be effective in a small number of cases but are rarely used. Immobilization of the cilia (the rate of movement of a foreign particle by the cilia is about 1 inch per minute) by the oil is a strong contraindication. However, it is recognized that a few patients with such conditions as bronchiectasis do occasionally ob-

tain temporary relief. Adequate supervised postural drainage is a necessity after the instillation.

Antihistaminic drugs number more than 100 and are characterized by an indefinite knowledge of which one to use on any patient. One allergist gives his patients the entire list with instructions to use one after the other until he finds one that gives the desired effect. The relief is only temporary in any case. Boyd[27] states after observing a large number of cases that the routine use of antihistamine drugs in routine antitussive remedies is not justified. He found they are not beneficial in the common cold. They should be reserved for use only in allergic manifestations. Prigal[28] described the characteristics of an allergic cough as loud, barking and paroxysmal in nature. It is relatively non-productive and lasts an indefinite length of time. The allergic cough rarely requires as much treatment as the other symptoms produced. For this reason ACTH and cortisone and their derivatives are rarely mentioned as cough remedies although they are used frequently in the treatment of the over-all condition.

Radiation Therapy. The indications for the use of x-ray therapy and the method of its administration has not changed for many years. It is usually reserved for those cases which fail to respond to other forms of treatment. Radiation for chronic infections in the sinuses and throat aids in stopping the postnasal drainage that produces a large number of chronic coughs. Mild radiation over the lungs destroys a certain amount of lymphoid tissue. It is theorized that this breaking down of the lymphoid tissue liberates a protein-like substance. Relief from symptoms is slow in this type of treatment and the delay should be explained to the patient.

Teaching the Patient. Time and thought should go into the personal instructions to each patient. This is just as important as medication. Personal care is important in the management of chronic coughs. Patients should be instructed to keep outside windows in sleeping quarters closed in damp or cool weather. They should avoid changes in temperature as much as possible. They should wear warm sleeping apparel at night and warm clothing during the day. They should avoid drafts both at night and in the daytime, and should avoid dust or other irritating inhalants at all times. Exercise may well be restricted and smoking should be discontinued. If possible they should avoid others who have respiratory infections. Regular habits at all times, and a maximum amount of mental and physical rest is helpful. Every effort should be made to go into the patient's home care problems. Coughing occurring in cardiacs responds extremely well to bedrest with digitalization, mercurial diuretics and a salt-free diet. These and other patients such as the bronchiectatic must be taught how to live. Most patients are ignorant of hygienic care and must be taught in detail.

Abdominal binders are advantageously used in emphysema and its attendant cough, but the patient must have specific instructions about the proper manner of applying them. Postural drainage is never a successful procedure unless the patient is repeatedly instructed in the proper methods and time. He should be taught that the sputum is better in a cup than in the lung, that the more noise the less effective cough, and that constant hacking and hawking only irritate and make his condition worse.

SUMMARY

1. Importance of cough as a symptom as viewed both from the health and economic standpoint is stressed. Pathology of the cough mechanism is simplified by describing the causes and effects of harmful and helpful coughs. Pathways of the cough reflexes are described. Tussal insufficiency and tussive syncope are discussed.

2. Surgical intervention, physiotherapy and postoperative prevention of atelectasis are discussed with reference to cough. The role of cough in emphysema is described. Common colds, "air conditioning" and the lack of acclimatization of the respiratory mucous membrane as a cause of cough are discussed.

3. Drug therapy including morphine and its derivatives is described. Bronchocatharsis and the use of such drugs as potassium iodide, ammonium chloride and others are described in detail. A few of the common combinations of cough remedies are listed. The use of antispasmodic drugs and gases, including the use of carbon dioxide, is enumerated. Positive-negative oxygen therapy in chronic pulmonary disease is reviewed and emphasized. Inhalations and aerosols are evaluated, and newer

liquefying aerosol combinations are described. Oils and antihistaminic drugs are discussed.

4. Radiation therapy and "teaching the patient" are discussed in detail.

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Relation of the Nose and Throat to Pulmonary Diseases

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IN the diagnosis and treatment of pulmonary diseases the chest physician encounters a number of symptoms that have their origin in pathologic conditions of the nose and throat. The specialists in thoracic disorders are confronted with symptoms such as cough, hemoptysis, excessive expectoration and others that may or may not originate in the chest. There are times when patients are treated for pulmonary abnormalities when in reality the symptoms are due to diseases in the nose and throat. For example a person may be treated for tuberculosis, bronchiectasis or bronchitis because his presenting symptom is cough or hemoptysis. However, if the symptom is thoroughly investigated, the cause would be found in the nose or throat. The opposite may also be true. The otolaryngologist may treat the symptoms as difficulties in the nose and throat when they really originate in the lung.

We wish to bring out in this discussion that an examination of the nose and throat by a competent otolaryngologist is important in investigating cough, hemoptysis and other symptoms.

Cough. The most frequently encountered symptom is cough. Infections anywhere in the upper respiratory tract may extend downward to produce inflammation and irritation of the trachea and bronchi accompanied by cough. It is true, too, that the cough may be a reflex one due to infection in the nose and throat without actually causing inflammation of the bronchi. We must remember that the mucous membrane of the upper respiratory tract is continuous with the bronchi, and an infection in one area travels readily to another.

There are certain areas in the nose that are very sensitive and may be irritated by mucus, congestion or fumes, by pressure of enlarged turbinates, and by contacts with a deviated septum. This irritation may cause a reflex type of cough. The treatment is to remove the cause of the nasal irritation. The presence of mucus and the congestion of the mucous membrane may be due to allergy or to infection and must be treated accordingly. Enlarged turbinates may be reduced in size by cauterization or by partial resection. Removal of pressure contacts of a deviated septum is accomplished by performing a submucous resection of the nasal septum.

"Catarrh," or postnasal drip as it is more commonly called, may also produce a cough. The discharge may consist of mucus, pus or mucopurulent exudate. A mucopurulent exudate, which is most probably due to sinusitis, may drip into the trachea and thus cause tracheitis or bronchitis and cough. This condition can be improved only by treating the sinuses. This may be done by nasal shrinkage, by irrigation or by antibiotics. Should these methods fail, more radical means involving operative procedures may be required in order to permit drainage of the purulent material or to remove infected mucous membrane lining the sinus.

A non-purulent mucous secretion resulting from a deviated septum may afford the same symptoms. Coughing may be the result of any type of nasal obstruction. Allergic rhinitis or vasomotor rhinitis of long duration as well as chronic infection may terminate in hypertrophic turbinates. Shrinkage and relief of the obstruction can be attained through scarring by cauterizing the turbinate. In the case of allergic rhinitis appropriate treatment can be given only after the cause of the hypersensitivity has been ascertained. Vasomotor rhinitis when not due to hypersensitivity may be traced to other factors such as menopause, fibroid uterus, ovarian dysfunction, emotional upsets, diabetes, etc. Although postnasal drip is a common complaint, when it produces a cough the source of the trouble may be difficult to trace.

Infection or enlargement of the tonsils and adenoids often produces cough, especially in

children, and immediate relief is obtained by their removal. Regrowth of nasopharyngeal lymphoid tissue causing cough may be removed either by surgery or radiation therapy. This regrowth of tissue may be on an allergic basis, usually bacterial sensitivity due to infection in the excessive lymphoid tissue. However, other sensitivities must be investigated also. Dryness due to mouth breathing as a result of nasopharyngeal obstruction may also cause coughing in children.

A cough may be caused by inflammation and enlargement of lateral lines of lymphoid tissue situated behind the posterior pillars of the pharynx. This lymphoid tissue may be removed or treated by cauterization.

The sensation of irritation or of a lump in the throat, most marked when a patient is lying down, may produce a cough and may be due to enlarged lingual tonsils. Again, removal or cauterization relieves the condition. If the lingual lymphoid hyperplasia is caused by chronic sinusitis and its postnasal discharge, the sinuses must also be treated.

Inflammation of the mucous membrane of the upper respiratory tract is frequently produced by excessive smoking. Irritating fumes encountered in certain occupations may create a cough. Congestion of the mucous membrane of the larynx and pharynx may be due to alcoholism. An elongated uvula resting on the base of the tongue can cause an annoying cough. Aspiration of food or fluid due to motor or sensory paralysis of the pharynx and larynx can produce coughing. Likewise, esophageal stenosis or pharyngeal diverticulum may cause overflow of material into the larynx. Any type of tumor along the respiratory tract, particularly in the hypopharynx or larynx, may result in a cough either by irritation or aspiration.

A prominent causative factor in cough is allergy. There is swelling and congestion of the mucous membrane throughout the nose and throat, giving a sensation of irritation and stuffiness. Often after an acute upper respiratory infection the cough persists. This could be due to an allergic type reaction to infection and should be treated by intranasal shrinkage and antihistamine therapy.

To summarize, if the lung is found to be free of pathologic disease, a persistent cough may be cured by proper treatment once the cause is ascertained and traced to the nose and throat.

Hemoptysis. Whenever hemoptysis is present and an x-ray of the chest proves to be negative, the upper respiratory tract should be thoroughly investigated. Expectoration of blood may result from rupture of varices in the postnasal space, pharynx or at the base of the tongue. When irritated by acute or subacute infections, the varices may bleed on coughing. Benign or malignant tumors of the nasopharynx, pharynx, base of tongue or larynx may be a source of bleeding. Telangiectasis may be another possibility, and frequently bleeding gums are a source of blood-spitting. In any case in which no pathologic condition can be found in either the upper respiratory tract or the lung, bronchoscopy should be performed to determine the origin.

Expectoration. It is difficult to determine whether expectoration of purulent or nonpurulent material comes from the lungs or upper respiratory tract, and both must be investigated. Examination of the upper respiratory tract, especially the nose and sinuses, is imperative to discover the origin of a postnasal drip which may strike the larynx and be coughed up. This discharge may accumulate in the trachea during the night and produce expectoration and cough in the morning.

Fetid Odor. There are many causes of this complaint which may or may not accompany cough and expectoration. A purulent sinusitis that is otherwise silent may produce a fetid odor to the breath. An abscessed tooth extending into the maxillary sinus produces a purulent sinusitis partially caused by anaerobic organisms. Infection may involve the mucous membrane of an antrum following a tooth extraction causing an extremely foul odor. A very frequent cause of foul breath is infection in the lymphoid tissue at the base of the tongue. Ozena or atrophic rhinitis also produces a fetid odor. Poor dental hygiene and mycotic infection in the lymphoid tissue of the pharynx, faucial tonsils and lingual tonsils may cause fetid breath, and cauterization or removal is required.

Dyspnea and Wheeze. A careful history is important in differentiating between nasal obstruction and dyspnea. A patient will say that he cannot breathe or cannot "catch his breath" when actually there is some obstruction to the air passage in the nasal cavity.

Laryngeal obstruction by a tumor, paralysis of a vocal cord, edema or cicatricial stenosis following trauma to the larynx may result in a

wheeze that is heard in the chest. Congenital stridor due to infantile type larynx or congenital web or foreign body must be considered in children. In some cases of wheezing, laryngeal examination is imperative.

Sinobronchitis. Some diseases of the lung are directly related to pathologic disease in the nose and throat, for example the syndrome of sinobronchitis. Persistent or recurrent bronchitis often is traced to infection in the upper respiratory tract, particularly the sinuses. Sinusitis may either act as a focus for the disease in the bronchi, or the infection may involve the mucous membrane of the bronchi by direct extension. Pus dropping from the nasopharynx into the trachea may also cause inflammation of the bronchi. Bronchitis may follow acute nasopharyngitis without involvement of the sinuses. These upper respiratory infections may be prevented by the use of autogenous or stock vaccine in an effort to increase resistance to infections and thus reduce the possibility of recurrent attacks of bronchitis. Tonsillar infections may extend to the bronchi, and only by tonsillectomy will the chronic or recurrent bronchitis be cured.

Bronchiectasis. There are different trends of thought concerning the relationship of bronchiectasis to sinusitis. Some believe that the basic causative factor of both conditions is allergy, especially sensitivity to bacteria, and that both conditions occur simultaneously. Others contend that chronic sinusitis produces the conditions which lead to bronchiectasis. However, there are many instances of bronchiectasis where the sinuses are perfectly clear, and certainly sinusitis may be present without bronchiectasis. It has been found that proper treatment of the sinuses will frequently alleviate some of the distressing symptoms of bronchiectasis. It must be remembered that aspiration of purulent discharge may produce bronchial obstruction which may, after a time, lead to bronchiectasis.

Asthma. Infection in tonsils and adenoids, especially in children, may be the causative factor of still another symptom—asthma. It is sometimes considered a bacterial sensitivity. At times there is a regrowth of lymphoid tissue following tonsillectomy and adenoidectomy which, when infected, produces the asthma. Surgery or radiation therapy to shrink the affected tissue attains relief of the condition.

Sinus infection in adults may account for the complaint of asthma. Frequently there is a suppurative process in one or more of the sinuses or polyp formation in the nose. Various conservative and radical procedures may be indicated depending on the extent of the pathologic condition. Allergic individuals may have swelling of the mucous membrane of the sinuses but no infection therein, and therefore operative removal will not aid the condition and might tend to create chronic nasal invalids. Only when pus and abscess formation is demonstrated in the mucous membrane is surgical intervention advised. This may range from simple nasal polypectomy or straightening of deviated septa that prevent proper drainage of the sinuses to the more radical type procedures as indicated. However, since the latter may aggravate asthma, it is most important to determine the state of infection at time of examination and by x-ray, and chose the most conservative yet effective treatment.

SUMMARY

Since certain conditions of the lungs and bronchi may originate in pathologic disease in the upper respiratory tract, the otolaryngologist can be of great assistance to the chest specialist or internist in investigating these conditions and in determining the origin of such symptoms as cough, hemoptysis, expectoration, asthma etc. Thorough work-up and competent treatment of abnormalities of the nose and throat may explain many symptoms attributed to the lungs and may cure some pulmonary diseases.

Postoperative Pulmonary Complications*

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POSTOPERATIVE pulmonary complications occur when obstruction develops in the lumen of the bronchial tree or in the blood vessels of the lung. The bronchial obstruction is commonly due to the patient's failure or inability to rid himself of his own secretions but may result from the aspiration of foreign material, such as blood, gastric or intestinal secretions or tissue. It is generally held that the usual vascular accident is the lodgment in a pulmonary artery of an embolus or emboli formed of thrombi displaced from peripheral vessels. There is, however, another school of thought which contends that a more frequent occurrence is primary thrombosis in the pulmonary artery. Cummine and Lyons[1] have advanced this hypothesis, and Dew[2] of the same school has only recently supported this point of view and suggested that efforts to prevent pulmonary embolism by the ligation of peripheral veins have failed because they were founded upon a wrong concept.

It is fortunate that many of the measures which can be employed to lessen the incidence of bronchial complications are equally important in reducing the frequency of vascular occlusion. For the sake of clarity it is necessary, however, to discuss the two conditions under separate headings.

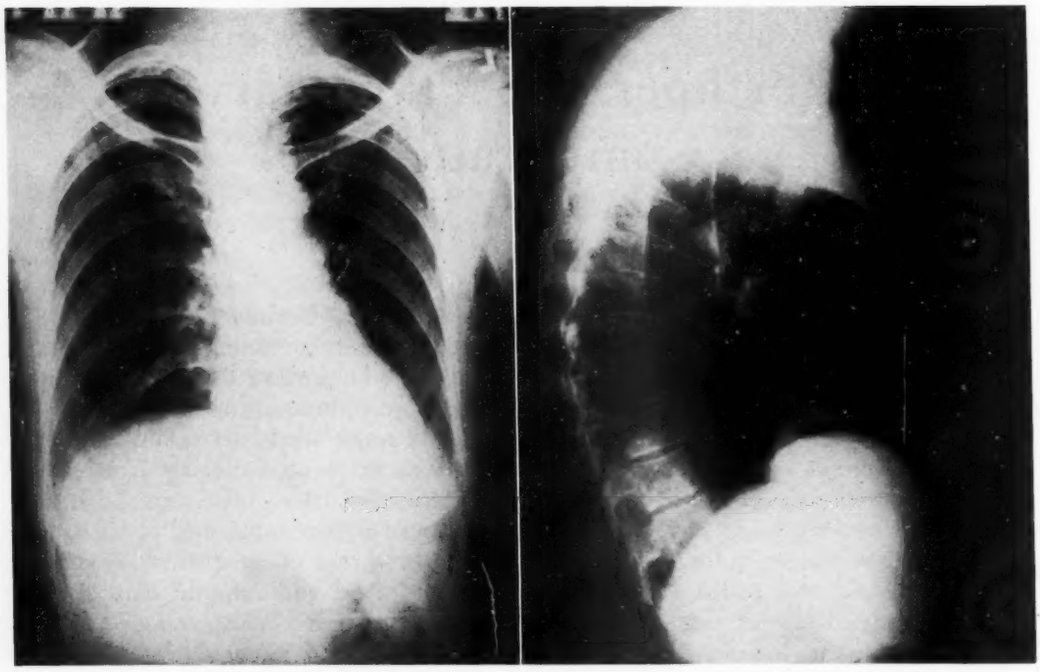
ATELECTASIS

The term "atelectasis" was used first by Jorg in 1835. In 1811 Schenck described what would now be interpreted as atelectasis of the lungs in children dying shortly after birth. In 1828 M. Louis recognized in adults the condition which we know now as postoperative pulmonary atelectasis. Clinical interest in the condition may be said to date from William Pasteur's presentation in 1890[3] and, on this continent wide recognition was given to the publication of Scrimger in 1921.[4] It took some time to establish bronchial obstruction as the causative factor and to differentiate the condition from pulmonary embolism.

It is more likely to occur in men than in women; in those suffering from an acute or chronic bronchial disease, including that produced by smoking; and at least in northern climes, in the winter than in the summer months. Age and chronic debility contribute to its occurrence. It is far more common after abdominal, and particularly upper abdominal operations than after other procedures. Pulmonary edema, which is more likely to occur in cardiac insufficiency, in burns and probably following chest trauma, aids in its development.

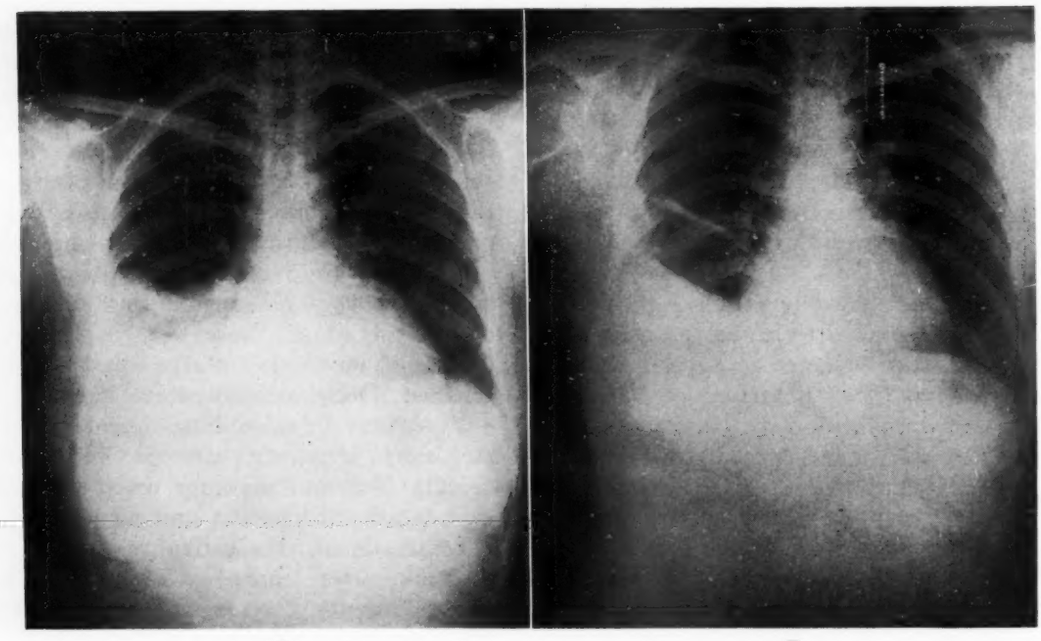
Diagnosis. Recognition of the condition depends primarily upon familiarity with its clinical picture and an awareness, particularly on the part of the house staff, of the necessity for attention to the chest in the postoperative period. An elevation of temperature, pulse and respiration within forty-eight hours after operation is the warning sign. There may be a vague sense of dyspnea or inability to fully aerate the lung. There may or may not be decreased movement of the chest on the side affected. Decreased resonance is usually present but may be difficult to detect. Diminished air entry is always present and there are usually fine and medium moist rales in the early stages. Elevation and some decrease in movement of the diaphragm is almost the rule after upper abdominal procedures. Great difficulty often arises in deciding whether the patient is suffering from atelectasis alone or atelectasis which is a complicating factor of a subphrenic collection. In a gross lesion the screen and x-ray will confirm the diagnosis but in a diffuse patchy lesion due to the blocking of many small bronchi, the clinical findings are more important. Many such cases of patchy atelectasis are undoubtedly diagnosed

* Read before the American College of Surgeons, October 7, 1953.



1A 1B

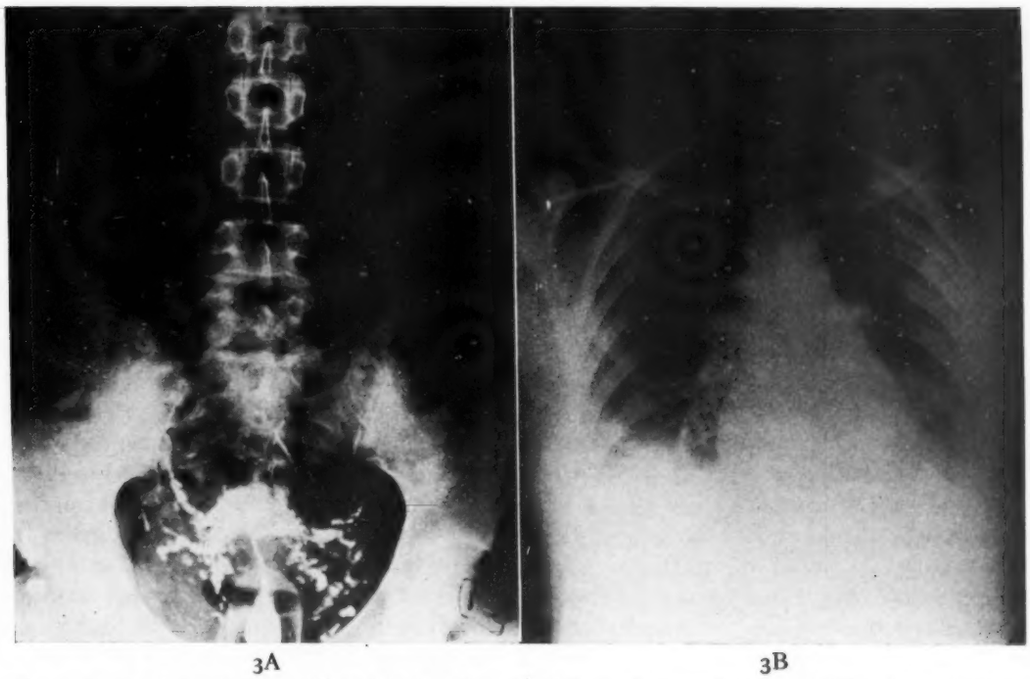
FIG. 1. A and B, postero-anterior and lateral films showing classic left lower lobe atelectasis.



2A 2B

FIG. 2. A, pulmonary embolism three weeks after hysterectomy. B, same case, two weeks later.

as chronic bronchitis while the more massive lesions are still all too frequently labeled as postoperative pneumonia. Bronchopneumonia is almost inevitable if the block cannot be removed from the bronchus, but it is not the primary lesion. Should pneumonia supervene, a small proportion of cases will develop abscess and bronchiectasis or both. Occasionally when there is a massive block of a lower lobe or even a main bronchus, the onset is sudden and severe with great respiratory distress, cyanosis, great anxiety and a sense of impending death.



3A 3B

FIG. 3. A, uterine injection of lipiodol after the completion of a menstrual period. B, chest film four days later showing lipiodol in lung. Clinical picture of pneumonia.

such cases may be difficult to distinguish from massive embolism. Mortality from atelectasis is small, but the morbidity associated with it is great. (Figs. 1 to 3.)

PROPHYLAXIS

The Preoperative Period. Patients suffering from acute respiratory infections should not be operated upon unless operation is imperative. It is probably wise to postpone operation for two to three weeks, although with the use of antibiotics a somewhat shorter interval may suffice.

The smoker with chronic bronchial irritation should stop smoking for a period of at least two to three weeks, and if the bronchial changes are severe, somewhat longer.

Patients with bronchiectasis or severe chronic bronchitis should be placed upon postural drainage for ten days to two weeks. In those patients with copious sputum this is best accomplished by a period upon an inclined frame with the head 15 to 18 inches lower than the feet. Antibiotics should usually be given.

It is the patient with thick tenacious sputum who is particularly liable to atelectasis, and for that reason one doubts the wisdom of giving atropine. It is better to give expectorant mixtures which liquefy the sputum and make it easier to raise or to use a steam tent in the pre- and postoperative period.

Operations upon a patient with a full stomach should be avoided. If an anesthetic must be given too soon after food, a stomach tube should be passed and, particularly in the presence of intestinal obstruction, a duodenal tube should be utilized during the operation.

The necessity for deep breathing in the postoperative period and the need for coughing to clear secretions should be discussed with the patient before operation, particularly in those thought likely to develop chest complications. The use of preoperative breathing exercises which will be continued in the postoperative period is undoubtedly valuable.

The Anesthetic. There would appear to be no evidence that inhalation anesthesia carries a greater risk of postoperative atelectasis than does spinal anesthesia. An unusually high incidence after inhalation anesthesia is more likely to be related to poor preoperative preparation, inexpert administration of the anesthetic and inadequate postoperative care. Similarly, the anesthetic agent seems to make little difference. The use of local anesthesia may lessen the danger but does not remove it.

The lightest level of inhalation anesthesia that is adequate for the surgical procedure

would seem desirable. The anesthetic agent should be stopped as soon as possible in order that the cough reflex may return shortly after completion of the operation. Heavy preoperative sedation, and particularly the use of long-acting barbiturates, should be avoided. Spinal anesthesia in association with long-acting heavy sedation is undesirable.

Aspiration of mouth secretions or intestinal contents should be avoided by the use of suction. In cases in which the danger is great, it is wise to depress the head of the table so that secretions will gravitate into the mouth where they may be aspirated. In operations on the upper air passages, mouth, and throat aspiration of secretions or blood into the trachea should be prevented by the use of an intratracheal tube with a cuff or packing in the pharynx.

Following many operations upon the chest, and always when there is any question of the presence of secretions or blood in the tracheobronchial tree, the air passages should be cleared by suction; and if there is any doubt, a bronchoscope should be passed before the patient leaves the table.

The Postoperative Period. The introduction of recovery rooms to which all patients are returned from the operating room has reduced pulmonary complications. Skilled attention from specially trained personnel is always available together with all necessary equipment.

Whenever possible, patients should be placed in bed upon their side, not upon their back, when they leave the operating table and preferably the foot of the bed should be raised. In this position secretions gravitate into the mouth and may be sucked out when necessary. Sedatives should be withheld until bronchial secretions have been cleared by coughing. Deep breathing and coughing should be insisted upon at frequent intervals. It is apparently true that morphine depresses the activity of the cilia in the bronchial tree, but few patients will breathe deeply or cough if the efforts are too painful. The necessity for deep breathing and coughing should have been explained before operation. I have always believed that the use of adequate sedation is desirable, provided the patient co-operates and does deep breathing and coughing ten to fifteen minutes after the sedative has been administered. While adhesive strapping and binders should not be applied in such a manner as to restrict movements of the chest and diaphragm, moderate support lessens the pain of coughing and imparts a sense of security. Carbon dioxide inhalation is useful in those patients who otherwise refuse to cough and breathe deeply, but it should not be used as a substitute for good nursing control. Particularly in chest cases intercostal nerve block should be used when pain is interfering seriously with the clearing of secretions. Gastric and intestinal suction tubes undoubtedly increase nasal, pharyngeal and tracheal secretions, but their value in controlling distension outweighs these disadvantages. Their use should be discontinued, however, as early as possible. In certain cases the prophylactic use of antibiotics is advisable. Finally, active movement in bed and early ambulation tend to lessen the incidence of chest complications. Elevation upon a Gatch frame undoubtedly makes the clearing of secretions more difficult, interferes with aeration of the lung bases and encourages immobility. The nurse should not be allowed to elevate the Gatch frame for longer than half-hour periods until the patient is moving actively in bed, and preferably not until he is getting out of bed.

Treatment. If the condition is recognized in its early stages, re-aeration can be accomplished as a rule by more energetic coughing and deep breathing, if necessary with the use of carbon dioxide. The patient should be made to lie upon the opposite side and encouraged to cough forcibly while the chest and abdomen are supported by the hands of the attendant. Continuous short hacking coughs are useless and merely tire the patient. In certain cases the use of catheter suction as advocated by Haight is useful. If these attempts are not successful within a relatively few hours, particularly if the area is large, bronchoscopy should be employed. Bronchoscopy becomes necessary fairly frequently in postoperative chest cases and following severe chest injuries and head injuries, but should be required rarely in others. If the obstructing material is not removed early, extensive blocking of the smaller air passages develops, air is absorbed from the lung distal to the obstruction and no force can be developed to dislodge the offending material. Re-expansion under such circumstances is certain to be slow and infection is likely to enter by way of the bronchi. If antibiotics are not being given when the lack of aeration is recognized, they should be started

at once. It is best to prevent atelectasis by suitable prophylactic measures and failing this, to recognize it in its early stages when it can be relieved as a rule by a somewhat more energetic application of the simpler measures. Every nurse should be taught the importance of deep breathing, coughing and active movements of the extremities and should realize that it is her responsibility to insist upon these measures being carried out. If the patients are given a reasonable explanation of why these exercises are necessary, they will, with few exceptions, co-operate. It is in those exceptions, for the most part, that the use of carbon dioxide becomes necessary.

VASCULAR COMPLICATIONS

The tendency to thrombosis in the postoperative period is probably related more to immobilization in bed than to any specific changes in the blood or vessels as a result of the operation. Analyses of the cases of thrombosis from various hospitals have shown that the condition is not, in fact, more common in patients upon surgical than medical wards. It occurs more frequently with advancing age and patients with debilitating diseases, particularly cancer, are more susceptible to it. The slower movement of the blood in those with inefficient heart action seems a definite predisposing factor, and in relation to this a period of prolonged uncontrolled operative and postoperative shock would appear to increase the likelihood of its occurrence. Strangely, so far as I am aware, prolonged operations during purposely produced periods of hypotension have not increased its incidence. Infection was thought at one time to be a predisposing factor but no noticeable decrease in frequency over a number of years became evident with the virtual elimination of infection. The liberation of thromboplastin from damaged tissues and the increase in platelets and fibrinogen in the postoperative period would seem important. The greatest tendency to thrombosis is present seven to ten days after operation, however, and not in the immediate postoperative period. Furthermore, thrombosis of major vessels is uncommon after the major tissue injury of thoracoplasty; certainly it is no more frequent than after appendectomy and herniotomy. Increased viscosity of the blood whether from polycythemia or simple dehydration is apparently a contributing factor. On the other hand, uncontrolled anemia and low blood volume seem to increase its incidence. Confinement to bed in the preoperative period increases the danger.

It is apparent, therefore, that although no specific factor can be held responsible for the occurrence of thrombosis, it has occurred more frequently under certain conditions. In the preoperative period excessive concentration of the blood should be overcome, anemia and low blood volume should be corrected, infection should be controlled if possible and a good heart action should be encouraged. Reasonable activity should not only be permitted, but also insisted upon up to the time of operation. During operation unnecessary tissue injury should be avoided and blood loss should be substituted for by transfusion. Prolonged pressure upon the calves of the legs with the possible damage to endothelium should be avoided and when used, stirrups should cause the least possible interference with vessels and circulation in the legs.

In the postoperative period the very things that have been suggested to decrease bronchial complications are important in lessening the incidence of thrombosis—frequent change of position, if possible with the active participation of the patient, and deep breathing which improves venous circulation in the chest. In addition, there should be active movement of the limbs, particularly the ankles and toes, since this pumps the blood out of the veins of the legs and maintains an active circulation. Fowler's position should not be allowed until such time as the patient is moving freely without assistance, and preferably not until he is out of bed. Under all possible circumstances the patient should be out of bed and taking a few steps about the bed within twenty-four to forty-eight hours. Leithauser insists that this is too late and that all patients should be out of bed the day of operation.[5] When he is up he should not be permitted to sit inactive in a chair for more than short periods of twenty to thirty minutes.

Treatment. If the usually recognizable evidences of thrombosis in the peripheral veins appear in spite of these precautions, the administration of anticoagulants is usually indicated. When evidences of thrombosis are minimal and confined to the calf muscles the application of an elastic bandage and continued exercise and ambulation, as advocated

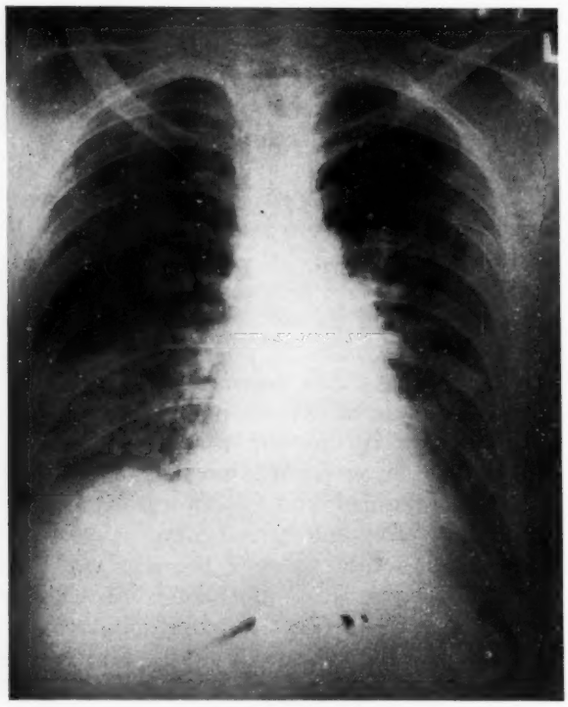


FIG. 4. Fat embolism.

by Leithauser, seems effective and is probably safe.[5] The ligation of major veins in an effort to prevent pulmonary embolism does not seem to have been effective; and although perhaps justifiable occasionally, it should not be undertaken lightly. The Sydney school, of course, maintains that it has no place because the peripheral manifestations are only part of changes which are also present in the lung.[2]

The diagnosis of a frank pulmonary embolism is not difficult as a rule, although without doubt, many lesser cases of infarction are not recognized. One must accept the possibility that embolism is confused with thrombosis on occasion. If thrombosis within the lung is common, it may be confused with atelectasis at times, but in general atelectasis occurs early in the postoperative period and the vascular changes, late. Chest films confirm the clinical history and findings in many cases, but there may be no recognizable changes in the x-ray in the early stages of quite extensive infarction.

Treatment consists of the use of anticoagulants and the reinstitution of activity as soon as possible. In the presence of massive infarction the congestion and swelling lead to a decrease in the size of the lumens of the bronchi and increased secretions. Stagnation of secretions makes it easier for pathogenic bacteria to enter by way of the bronchial tree and set up an infection in the devitalized area. For this reason the use of antibiotics is indicated.

FAT EMBOLISM

Fat embolism may be expected to occur following injuries to long bones, particularly fractures, and occasionally following operative or other trauma to areas in which there is an extensive deposition of fat. I venture to say that in the experience of most of us it has been recognized infrequently. On the other hand, Musselman, Glas and Grekin thought that 52 per cent of 109 injured patients probably had fat embolism.[6] Forty-one of 125 cases of fatal accidents studied by Robb-Smith showed evidence of gross pulmonary involvement.[7] The pathogenesis of the condition is still in doubt. It is suggested that embolism occurs when fat globules liberated from the supporting fibrous tissue of the bone marrow are sucked into torn veins. Gauss thought that the veins in the bone marrow were held open by the bony wall and unable to collapse as elsewhere.[7] Scuder thought the more toxic oleic acid was more likely to be responsible than neutral fat.[7] Harris, Perrett and McLachlin established that 0.9 cc. of neutral human fat per kg. of body weight was the lethal single dose for rabbits, but if repeated doses not exceeding 0.5 cc. each were used as much as 0.15 cc. per kg. of body weight could be given without death, although marked pulmonary signs and ataxia and incoordination were produced.[8]

The usual history is that of injury, most often a fracture, followed by a short interval (one to three days) in which the only symptoms are related to the injury. Pulmonary signs and symptoms develop and consist of cough and sputum with, at first, impairment of air entry and a few rales, and later consolidation. Cerebral changes appear; drowsiness, confusion and finally coma. Pallor is a striking feature; a hemoglobin level as low as 30 per cent was reported by Harris.[8] There is some evidence that shock adds to the seriousness of the occurrence. The cerebral changes rather than the pulmonary seem to be the cause of death. Many mild cases undoubtedly recover, having shown only minor pulmonary symptoms and cerebral confusion.

The diagnosis depends upon the history of injury, the related symptomatology, more or less characteristic radiographic chest find-

ings, the presence of fat in the urine in some cases, and in some, the finding of skin petechiae. (Fig. 4.)

Early immobilization of fractures is said to be prophylactic. Probably no treatment is very effective but the use of oxygen and antibiotics is said to be indicated.

LUNG ABSCESS

The majority of lung abscesses are caused by aspiration of infected material; a relatively small proportion are embolic in origin. In most series of abscess published some years ago 20 to 25 per cent followed operation, the majority of these operations being upon the upper air passages. A few follow aspiration of a major foreign body, such as a tooth, a crown from a tooth or a piece of tonsil. Usually, however, a minute portion of septic material lodges in one of the smaller terminal bronchi and it is not realized that there is anything amiss until, in an effort to discover the origin of persistent fever and perhaps pleural pain and cough, an x-ray is made. Occasionally at the end of ten days to three weeks a considerable volume of pus is coughed up, but more frequently there is a gradual increase in the amount of sputum raised. Aspiration of a considerable quantity of gastric or intestinal contents may induce pneumonia of a septic character and eventually multiple abscesses. The mortality from such accidents is high.

A lung abscess may be produced by a sterile or septic embolus. In the latter case the abscess contains at first only a single organism, for example, Staphylococcus aureus, derived from a focus of osteomyelitis. In the former an originally sterile infarct becomes infected with mouth organisms by way of the bronchial tree and the abscess contains the same mixed bacterial flora as though it had resulted from aspiration alone without the predisposing sterile infarction. As would be expected septic emboli are frequently multiple.

The prevention of aspiration of septic material depends upon careful preparation of those patients in whom the accident could be expected and the expert administration of the anesthetic. It is a wise precaution to give antibiotics to the patient known to have had a sterile infarction. The use of antibiotics and a minimum of trauma to septic areas will lessen the likelihood of septic infarction. Early recognition of the pneumonic focus and adequate antibiotic therapy will abort a high percentage of incipient or potential abscesses at an early stage. Lung abscess has now become a rare postoperative complication.

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Bronchoscopy in the Diagnosis and Treatment of Bronchopulmonary Disease

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Since the bronchoscope is a speculum similar to those used in various other fields of medicine to observe cavities and passages which are not otherwise visible, its limitations restrict the bronchologist in the portion of the tracheobronchial tree that is accessible to inspection. While the trachea, larger bronchi and orifices of the different lobes with their major subdivisions are available for examination, the smaller bronchi and peripheral radicals cannot be seen. Telescopic inserts now enable the bronchologist to view previously hidden portions of the bronchial tree, but large segments still remain beyond his vision. Although these latter areas are not amenable to direct inspection, secretions and exudates can be obtained from these regions for bacterial and cytologic examinations. To be of value this material has to be collected from the precise subdivision leading to the disease. The examiner must be thoroughly conversant with intrabronchial anatomy in relation to the involved bronchopulmonary segment as localized on the roentgenogram to accomplish this.

The contraindications to bronchoscopy are few. Moribund patients and those with severe or advanced cardiac failure, untreated myasthenia gravis and lesions of the cervical spine in which hyperextension of the head might lead to compression of the spinal cord are not suitable candidates. Bronchoscopy should be avoided during critical pulmonary bleeding but should not be postponed too long and can be done with reasonable safety forty-eight hours after the acute bleeding episode has subsided. When performed soon after active bleeding, valuable information can be obtained, and bronchoscopic localization is often helpful in detecting the lobe or subdivision from which the blood originates. If one waits until there is complete subsidence of pulmonary bleeding, bronchoscopy may reveal nothing and the value of the examination in this respect is lost.

The greatest usefulness of bronchoscopy lies in diagnosis, and when positive and concrete evidence is uncovered the diagnosis is established. When a partial or complete obstructive lesion such as obstructive emphysema or lobar atelectasis is seen on the roentgenogram, bronchoscopic observation generally uncovers the cause. In these conditions appropriate treatment through the bronchoscope may, at times, be curative.

It is only within the past twenty-five years that bronchoscopy has come into general use and it is now an integral part of the examination of patients with pulmonary symptoms. Seldom is bronchoscopy necessary before the patient has had a complete medical examination and study; and if the patient has a chronic cough, a chest roentgenogram should always precede bronchoscopic investigation. The radiologist interprets shadows on the roentgen films and generally reaches accurate conclusions but because of this fact the nature of the lesion may remain obscure so that bronchoscopic study is needed in making the diagnosis. Even when the roentgen findings are clear-cut and the diagnosis seems reasonably certain, it is advisable and possibly mandatory to confirm the diagnosis by follow-up bronchoscopic examination.

Bacteriologic study of secretions obtained bronchoscopically has proved valuable in diagnosing some of the fungous diseases which exhibit variable and inconclusive roentgenographic pictures. In patients with histoplasmosis in which the only objective findings were ulceration and proliferation in the tracheobronchial tree the diagnosis has been made by examination of tissue removed at bronchoscopy.

When symptoms referable to the chest remain unexplained by the other available diagnostic methods, the bronchoscopic findings may furnish the clue needed to make the diagnosis. In indeterminate chest lesions in which the diagnosis remains in doubt after all meth-

ods have been exhausted exploratory thoracotomy becomes necessary.

Negative roentgen findings do not always rule out pulmonary disease. In some cases the roentgenogram is normal yet serious trouble is present. Chronic cough, hemoptysis, persistent wheezing and at times unrelieved dyspnea are symptoms requiring endoscopic investigation, and the diagnosis commonly becomes evident when one looks into the bronchial tree.

Bronchoscopy is always indicated in any case of chronic persistent cough with or without expectoration. The possible presence of carcinoma of the lung must always be seriously considered, even though the patient often attributes the cough to smoking. Unfortunately carcinoma of the lung is not limited to males nor to those individuals past middle age and may remain asymptomatic or produce atypical symptoms and roentgen findings so that the earliest and most significant symptom of chronic cough cannot be neglected.

Surgical treatment of carcinoma of the lung has continued to progress; and if patients with this disease are to have their chances of survival improved, early diagnosis remains essential. Bronchoscopic biopsy has retained a prominent place in the diagnosis but when a lesion is accessible for biopsy the surgeon finds repeatedly that the carcinoma is inoperable by virtue of extension or metastasis or both. It is the minute lesion located in the smaller bronchi in which curative results can be anticipated, and cytologic study of secretions from the involved bronchus has established a diagnosis in many instances when the lesion is beyond bronchoscopic vision. In reviewing 488 cases of carcinoma of the bronchus Clerf, Herbut and Nealon[1] noted that the diagnosis was made by biopsy in 31.5 per cent and by cytologic examination of bronchial secretions in 56 per cent, making a total of 87.5 per cent diagnosed by bronchoscopic and cytologic means. Even though there was a high percentage of positive diagnoses, pulmonary resection could be performed in only 42 per cent of the cases with a 27 per cent survival rate over a five-year period. While these figures are excellent in comparison with others, they need to be improved—emphasizing the fact that the curability of bronchogenic carcinoma is proportionate to the resectability rate which in turn is directly related to early diagnosis.

In some peripherally placed lesions it is possible to make the diagnosis by finding carcinoma cells in the bronchial washings. When the cytologic studies are negative and clinically the lesion resembles malignancy, it should be treated as such until proved otherwise. Dependency cannot be placed upon cytologic examination alone and in the face of negative studies equivocal chest lesions in which carcinoma is suspected but not proved require surgical exploration. Occasionally false positive cytologic reports are obtained but operation must be unnecessarily performed in the infrequent case of this kind in order to establish the diagnosis definitely and to rule out malignancy.

Bronchoscopic observation is valuable to the surgeon in determining the exact site and extent of the tumor. While tissue for biopsy or positive cytologic cell findings may not be obtained, fixation and rigidity of the involved bronchus offers presumptive although unconfirmed evidence of malignancy. Extension into the mediastinum as evidenced by immobility and broadening of the carina indicates inoperability. When the tumor is found to invade the trachea, it becomes necessary for the surgeon to plan his approach to include tracheal excision and reconstruction. The observation of laryngeal paralysis is likewise important in determining operability, although Ochsner[4] has reported a successful pneumonectomy with a six and one-half–year survival in a patient having recurrent nerve paralysis.

A positive diagnosis of adenoma of the bronchus or trachea can be made in over three-fourths of the cases by examination of tissue removed at bronchoscopy for microscopic study. The only other method of positive diagnosis is by surgical exploration. Because the adenoma is usually covered by intact mucous membrane the characteristic cells do not exfoliate and are not recovered in the sputum or bronchial secretions. Adenoma presents a characteristic bronchoscopic appearance of a smooth, non-ulcerated reddish mass which bleeds easily and occasionally is pedunculated. The differential diagnosis between adenoma and carcinoma may be difficult, but the selection of proper therapy is dependent upon accurate distinction.

Tracheobronchial tuberculosis is identified by bronchoscopic examination not only when the sputum persistently contains acid-fast bacilli in spite of adequate antituberculous therapy, but also when the sputum becomes

negative under treatment yet the patient fails to improve. Bronchoscopy provides a means of obtaining tissue for microscopic examination and bronchial secretions for acid-fast study. In the presence of stenosis secretion containing acid-fast organisms may pool behind the obstruction and aspiration of this material may reveal the causative organism whereas examination of sputum which originated above the stricture had consistently been negative. In tracheobronchial tuberculosis localized inflammation and edema of the mucosa about the involved bronchial orifice, the location and extent of pus, the presence of ulcerations and granulations, obstructive lesions and stenoses may be observed directly. In addition, in cases of bilateral tuberculosis one may obtain information regarding the source of the positive sputum and collect separate specimens from infected areas in each lung for examination to ascertain in which one activity exists. Bronchoscopy should always be performed prior to pulmonary surgery for tuberculosis to determine the presence or absence of tracheobronchial disease. The results of specific therapy in tuberculous bronchial lesions can be better evaluated by direct visualization during and after the course of treatment.

Hemoptysis is a symptom of pulmonary disease requiring bronchoscopic investigation. Besides carcinoma and tuberculosis a common cause of bleeding is bronchiectasis. While the diagnosis can be made by clinical, roentgenologic and bronchographic examinations, all patients with bronchiectasis whether active bleeding is present or not should have at least one bronchoscopic examination to rule out complicating factors, such as a foreign body which may have been aspirated in childhood and remained unrecognized or bronchial obstruction from a stricture or broncholith producing subsequent infection and bronchiectasis below the point of obstruction.

Bronchoscopy is a necessary procedure in any case of unexplained hemoptysis, for often direct evidence of a lesion that will account for the bleeding can be found. By tracing the blood to its point of origin a small lesion might be discovered, so that tissue or secretion can be obtained directly from the lesion or involved area thereby establishing an etiologic diagnosis which otherwise would not be possible. In a study of 200 cases of hemoptysis Moersch[3] found that the cause could not be determined in 75 per cent in spite of various diagnostic procedures; and when the etiology was unknown, it was his opinion that a serious pulmonary lesion would not develop subsequently.

Hemoptysis occurs in various forms of obstructive pneumonitis and middle lobe syndrome. The latter may be confused with pulmonary tuberculosis in younger individuals and carcinoma in older people; consequently bronchoscopy is valuable in differentiation. A frequent finding in obstructive middle lobe pneumonitis is pressure from an enlarged lymph node at the middle lobe orifice or the presence of a broncholith.

As a precautionary measure bronchoscopy should be employed in cases of chronic lung abscess, and even though the diagnosis is evident by physical and roentgen means the etiology is often obscure. Formerly, pulmonary abscess commonly followed operative procedures particularly under general anesthesia and about the head and neck, but now the most frequent cause is bronchogenic carcinoma. When a tumor becomes necrotic in the center, liquefication occurs and an abscess cavity forms, especially if the draining bronchus is blocked by tumor. Aspiration of secretion from the abscess area may reveal the presence of tumor cells. In acute inflammatory abscesses early treatment by bronchoscopic drainage and opening of the obstructed bronchus produces improvement and along with antibiotic therapy may be curative. Chronic abscess cannot be cured by this means, although establishment of drainage and removal of secretion may result in diminution of fever and general improvement in the patient's condition so that when needed surgical treatment can be performed with less risk.

One definite indication for bronchoscopy is in cases of stridor or wheezing respirations of unexplained etiology. It must always be remembered that wheeze means partial obstruction and, until the cause has been found, every avenue of approach should be exhausted. Tracheal and bronchial obstruction may produce symptoms of marked respiratory embarrassment without visible roentgenogologic changes, and the underlying cause may only be detected by visualization through the bronchoscope. The causes of bronchial obstruction are numerous and in addition to intrinsic lesions such as tumors, foreign bodies, strictures and stenoses extrinsic com-

pression of the trachea or bronchus may be observed from tumors, enlarged lymph nodes, vascular lesions or anomalies.

A superior mediastinal mass with displacement of the trachea on the roentgenogram may be due to substernal thyroid enlargement; but when dyspnea is present, bronchoscopy commonly reveals the true cause. In my experience substernal goiter rarely leads to significant dyspnea, and a thorough study is necessary to find the cause of the shortness of breath. On occasion lipoma, adenoma, carcinoma, lymphoma and tracheobronchial tuberculosis have been uncovered on bronchoscopic investigation.

Compression of the main bronchi from other extrinsic bronchial lesions may lead to obstructive signs and dyspnea. Mediastinal lymph node enlargement from metastatic carcinoma occurs frequently, but lesions of the lymphoma group, chiefly Hodgkin's disease, while less frequently encountered may be responsible for compression stenosis. At times, definite endobronchial involvement with ulceration and fungation exists, and in these instances the lymphomatous disease generally remains limited to the chest. Difficulty in obtaining sufficient tissue for histologic examination is the chief problem; and since these lesions closely resemble carcinoma clinically, the distinction is not easy unless histologic confirmation can be obtained.

Congenital anomalies are one of the principal causes of respiratory obstruction in infants and are responsible in many cases for respiratory emergencies. Holinger et al.[2] have stressed the need for correlation of the history, fluoroscopic, roentgenographic, bronchographic and bronchoscopic findings. It is not uncommon to have a young child admitted to the hospital with a diagnosis of atelectasis of the lung, which is found on subsequent study to be due to bronchial compression, either partial or complete, from anomalies of the heart and great vessels. At times, an erroneous diagnosis of atelectasis has been made when, in reality, the pathologic change was in the opposite lung which exhibited unrecognized obstructive emphysema from vascular pressure.

In children with respiratory difficulty bronchoscopy is a safe procedure provided no anesthesia is used, oxygen is administered, the instruments are small enough to prevent trauma, and the examination is carried out in a short time. Congenital anomalies that are suspected on the roentgenogram can be proved by bronchoscopic observation, which may reveal agenesis of the lung with or without a rudimentary bronchus, congenital webs, abnormal constrictions or bifurcations. Fibrocystic disease of the pancreas is manifested by respiratory symptoms in many cases; and when bronchoscopy is carried out, obstruction from secretion and inflammation is found.

While the role of bronchoscopy in treatment is secondary to that in diagnosis, it has proved helpful in the treatment of certain cases of bronchial adenoma, tuberculous tracheobronchitis, bronchial asthma, stenosis of the bronchus and atelectasis. In addition, bronchoscopy is unsurpassed for the removal of foreign bodies. It remains the only means by which this can be accomplished other than by exploratory thoracotomy. When the foreign body is peripherally located in the smaller subdivisions of the bronchi, fluoroscopic guidance is essential provided the object is radiopaque. In these instances the use of a magnetic instrument is limited because of the problem of making contact with the foreign body lodged in a distal pulmonary segment.

When a broncholith projects into the bronchial lumen producing bronchial obstruction, it may erode through the mucous membrane and, if so, can be removed bronchoscopically. It is unwise to incise an intact mucous membrane over the broncholith in order to extract it. Difficulty arises in removing the entire broncholith because of its fragmentary nature and usually portions have to be withdrawn piecemeal in order to overcome the obstruction and allow ventilation to the distal lung.

Stenosis of the bronchi with suppurative changes beyond the obstruction are thoracic surgical cases and are best handled by this means. In contrast, benign tracheal stenosis comprises a complicated problem, for the surgical approach has proved far from ideal. Even though repeated and prolonged endoscopic dilatation is required, this offers the best and safest method of treatment at the present time.

In tracheobronchial tuberculosis endoscopic applications of cauterizing agents may aid healing but far greater benefits are obtained with specific antimicrobial and antibiotic therapy. Granulation tissue which is causing bronchial obstruction should be extirpated and an attempt made to keep it at a minimum so that

suppuration and atelectasis does not develop below this point. When a stricture or stenosis forms as the end result of the healing process, dilatation by means of bronchoscopic bougienage may keep the bronchus patent and prevent subsequent suppuration and bronchiectasis in the distal lung. After bronchiectasis develops, surgical excision of the involved pulmonary segment is inevitable.

In some cases of bronchial asthma and occasionally in chronic bronchitis the large bronchi become blocked by thick tenacious secretion creating pneumonitis and signs of atelectasis. At bronchoscopy blockage to the bronchus may be observed and after secretion is aspirated and patency restored marked improvement in the respiratory symptoms takes place and the fever subsides. This complication is particularly prone to start in the subdivisions of the lower lobe bronchi. In certain other cases of intractable asthma in which the patient is unable to cough up his own secretions due either to inability to secure sufficient tussive squeeze or to bronchial collapse, bronchoscopic suction affords relief by elimination of retained secretions.

When there are respiratory complications of fibrocystic disease of the pancreas in children, obstruction may develop from extremely thick and viscid secretions along with a thickened granular mucosa. Bronchoscopic aspiration leads to symptomatic improvement but may have to be repeated to maintain bronchopulmonary drainage and enable the antibiotic agents to better exert their effect.

Bronchoscopy is a primary requisite in the treatment of postoperative atelectasis, especially after operations in the thoracic cavity. There can be no question but that massive atelectasis should receive immediate bronchoscopic treatment. The lesser forms of postoperative pulmonary atelectasis with generalized patchy involvement throughout one or both lungs may clear up under conservative treatment, provided the patient is not sedated and efforts are made to induce cough and get rid of retained secretions. If after twenty-four to thirty-six hours under this regimen there has been no appreciable response, bronchoscopic treatment should be promptly carried out.

Regurgitated material aspirated into the lung should be removed as soon as possible to prevent pulmonary collapse and ultimate infection. Although bronchoscopy is useful in clearing up infantile atelectasis of a severe degree, most newborn infants can completely aerate their lungs in a comparatively short period of time. Tracheal aspiration will commonly be sufficient to remove secretion from the airway; but when there is collapse of a lobe or lung, bronchoscopic treatment is indicated.

Benign tumors of the bronchi are not encountered frequently; and while it is possible to remove them through the bronchoscope by cutting, snaring or diathermy when they are attached by a small base, endoscopic excision does not cure suppurative disease distal to the lesion after irreversible changes have taken place.

Since the bronchial adenoma habitually has its smallest projection into the bronchus and a larger non-visible extension extrabronchially, it is usually best dealt with by operation which as a rule does not have to be as radical as that for carcinoma. However, there are certain cases representing a small proportion of the total in which the growth can be adequately removed and handled by bronchoscopic means, for the tumor is relatively slow growing and metastasizes late. Excision of a small pedunculated lesion in one of the main bronchi can be accomplished by endoscopic means and following electrocauterization of the base the patient may remain well for many years. In older individuals when the tumor is located near the carina and an exploratory thoracotomy cannot be performed for physical and medical reasons, bronchoscopic treatment may afford considerable relief and allow the patient to live out his normal span of life. The problem becomes more complicated when bronchial obstruction leads to atelectasis and bronchiectasis. In this type of case the only definitive treatment must be surgical excision when the patient's condition permits.

SUMMARY

Although bronchoscopy is used in the treatment of certain pulmonary conditions, this phase remains secondary to its aid in diagnosis. The information gained by bronchoscopy is particularly valuable in the diagnosis of (1) obscure pulmonary disease, (2) the etiology of bronchial obstruction both complete and partial and (3) the determination of the cause of unexplained pulmonary symptoms. While one cannot rely entirely upon bronchoscopy in

the diagnosis of bronchogenic carcinoma, it remains the best means of providing a positive diagnosis, usually by histologic and cytologic study of tissue and secretions, and determining preoperatively the limits of the growth so that operability can be ascertained. When used in conjunction with roentgenography, a greater insight is gained into the nature of pulmonary lesions and the establishment of a more exact diagnosis. In treatment the major benefits are derived from the relief of bronchial obstruction, whether due to foreign bodies, benign or semimalignant tumors, retained secretions or fibrous stenoses.

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Pulmonary Edema

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PULMONARY edema occurs when serous fluid escapes from the pulmonary capillaries into lung tissue, alveoli, bronchioles and bronchi. Acute pulmonary edema as a complication of surgery is found relatively infrequently at the present time, except in certain patients undergoing cardiac surgery. Since pulmonary edema is a very serious complication every effort should be made to prevent its occurrence.

Edematous lung tissue is voluminous and heavy, and it will pit when pressed. The alveoli and bronchi of the edematous lung contain serous or blood-tinged fluid which can be expressed from the cut surface of the lung.

Lymph fluid is formed by fluid transuded from the pulmonary capillary into the wall of the alveolus. Fluid transuded from the pulmonary capillary can be removed by the lymphatic collecting ducts or the fluid can move into the alveoli and bronchioles and then be expectorated. The pulmonary capillaries can reabsorb water and electrolytes but not plasma proteins.

Drinker demonstrated that pulmonary edema develops when lymph fluid forms in the lung faster than it can be removed by the lymphatic system. The osmotic pressure of 25 to 30 mm. of mercury exerted by the plasma proteins exerts a stronger force to retain fluid in the pulmonary blood vessels than the hydrostatic pressure of 10 mm. of mercury tends to transudate fluid into the loose lung paranchyma. The negative alveolar pressure on inspiration favors the transudation of fluid from the pulmonary capillaries.

Pulmonary edema has been studied from many aspects. In the dog Drinker has shown that anoxia will cause an increase in the lymph flow in the lung. The fluid is churned to froth in the alveoli and bronchioles thus increasing the anoxia which produces a further leak of fluid from the anoxic pulmonary capillaries. This mechanism is one of the major factors in producing pulmonary edema.

By means of cardiac catheter studies Cournand has demonstrated that a considerable increase in pulmonary blood flow can occur in the normal human without change in the pulmonary artery pressure. Riley et al. demonstrated a decrease in pulmonary artery pressure during exercise by a normal subject. The pulmonary artery pressure was found to rise with exercise with no increase in the pulmonary artery blood flow. In patients with mitral stenosis and mitral regurgitation (Draper et al.) the pulmonary capillary blood pressure was thereby increased and favored the production of pulmonary edema. McMichael found that in a normal individual the cardiac output increased 33 per cent when the position was shifted from the erect to the recumbent. Liljestrand et al. and Nylin found that work caused no increase in heart size and no increase in vital capacity in the normal patient, but heart size increased and vital capacity decreased when a normal person shifted from the erect to the recumbent position. It has often been stated that pulmonary edema may occur when the left ventricle pumps more blood per minute than the right ventricle, thereby producing pulmonary blood vessel engorgement. Altschule reviewed this problem in 1954 and found no evidence to support this thesis.

Eaton found that the lung lymph flow was doubled in forty-five minutes following a hemorrhage of 25 per cent of the blood volume in the dog. If intravenous saline infusion followed the hemorrhage, the lung lymph flow increased markedly; but if blood or plasma followed the hemorrhage, the lung lymph flow was not elevated. Pulmonary edema was found in the dog given excess blood by Beattie

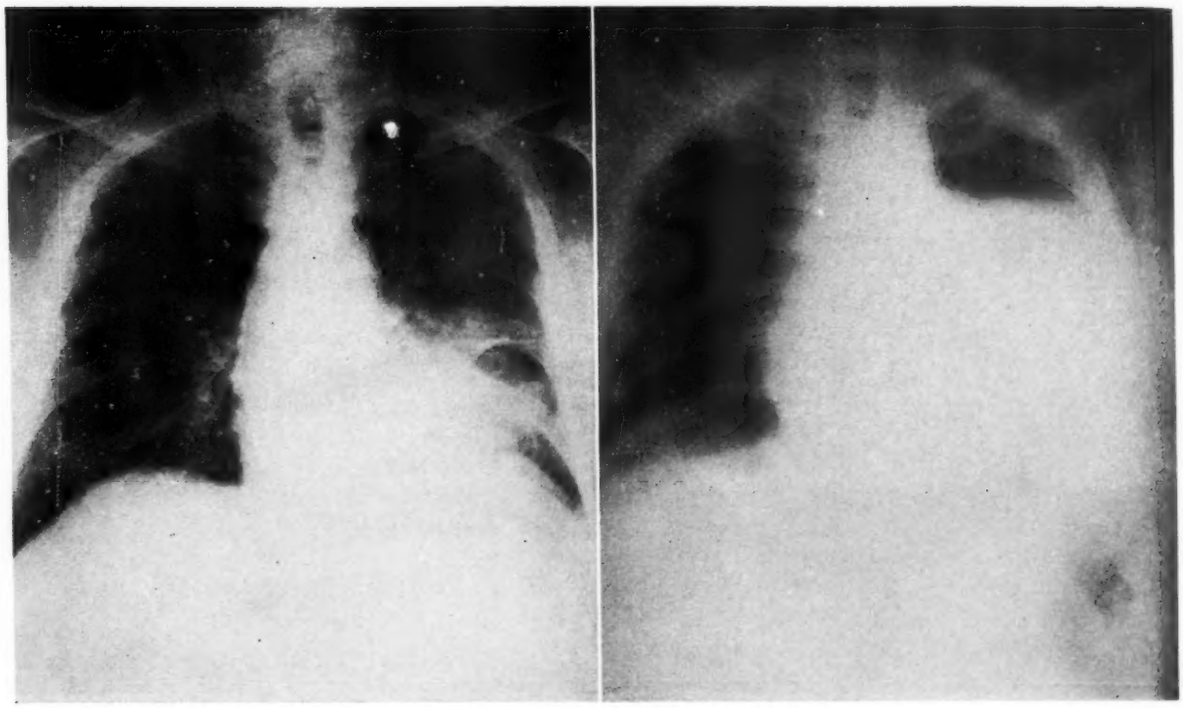

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FIG. 1. Chest roentgenogram of sixty-eight year old patient with bronchogenic carcinoma of the left lung before operation.

FIG. 2. Chest roentgenogram of patient in Figure 1 taken three days after pneumonectomy. Part of the pericardium was removed because of invasion of tumor. Intractable pulmonary edema occurred on the first postoperative day even though minimal blood and intravenous fluids were administered. Patient died on the third postoperative day presumably due to acute cor pulmonale following pneumonectomy.

et al. Altschule et al. and Heyer et al. showed that intravenous fluids increased heart size and decreased vital capacity. Luisada found that intra-arterial saline infusions in the normal dog equal to 230 per cent of the blood volume caused pulmonary edema. Pulmonary edema can occur with normal or increased body water. Stead cited the situation in which a normal individual developed acute pulmonary edema following a massive myocardial infarction. This is in contrast to the cardiac patient who slowly accumulated excess body water during a period of weeks. Edema in the latter instance is probably due to inadequate renal excretion of sodium chloride.

In summary, the chief factors concerned in the production of pulmonary edema are: (1) increased pulmonary capillary permeability, usually due to anoxia; (2) increased hydrostatic pressure in the pulmonary capillaries; and (3) decreased osmotic pressure of the blood. The tendency of the nephritic patient with lowered serum proteins to develop pulmonary edema is well known. Excess intravenous fluid will exert some of its adverse effects by diluting the blood proteins. Altschule has suggested an additional three factors which may be important in the increased transudation of lymph fluid in the lung: (1) bronchospasm, (2) increased pulmonary blood flow and (3) increased filtering areas in the lungs.

Conditions producing passive pulmonary congestion were classified by Lombardo as follows: (1) Conditions producing mechanical interference with left ventricular filling; for example, mitral stenosis, tamponade, an intrinsic mass in the left atrium and an extrinsic mass compressing the left atrium or pulmonary veins. (2) Conditions weakening the left ventricle, including structural disorders such as infarction and inflammation, or functional disorders such as anoxia or tachycardia. (3) Conditions increasing the work of the left ventricle, including disorders such as hypertension, aortic stenosis, coarctation, aortic insufficiency, mitral insufficiency and thyrotoxicosis.

Pulmonary edema results from an imbalance between transudation of lymph fluid and

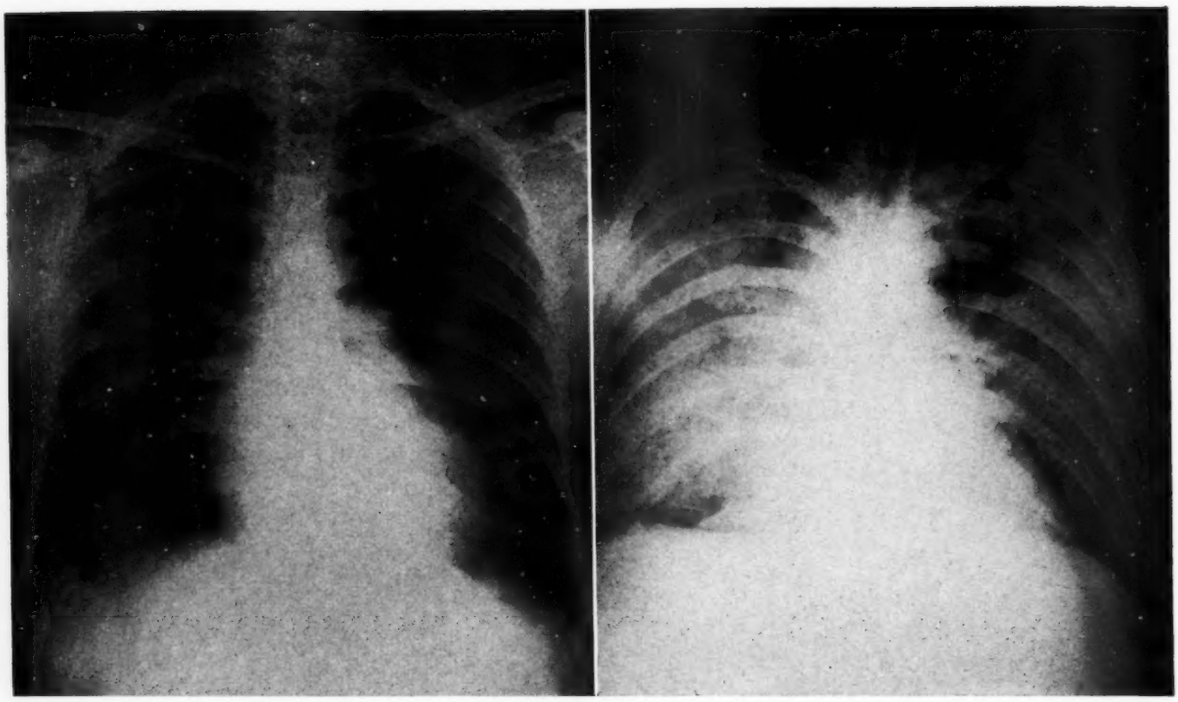

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FIG. 3. Chest roentgenogram of cardiac patient before going into acute pulmonary edema.

FIG. 4. Chest roentgenogram of patient in Figure 3 in acute pulmonary edema.

reabsorption of lymph fluid. Any factor which decreases reabsorption of lymph fluid in the lungs will of course favor the production of pulmonary edema. Since lymphatic vessels from the lung empty into the systemic veins an elevated systemic venous pressure will have an adverse effect upon reabsorption of transuded lymph fluid from the lungs.

Pulmonary edema can be recognized clinically by: (1) onset, gradual or sudden; (2) oppression or pain in the chest; (3) apprehension; (4) dyspnea or orthopnea; (5) incessant short cough with copious frothy or blood-tinged sputum; (6) pallor; (7) perspiration; (8) rales throughout lungs; (9) blood pressure and pulse rate elevated in severe cases; (10) blood pressure depressed in severe cases.

The clinical picture of pulmonary edema varies with the severity of the attack. Paroxysmal dyspnea occurs in the patient with hypertension, coronary disease or aortic valvular disease. This is acute pulmonary edema in mild form. A moderately severe form of pulmonary edema can be recognized as cardiac asthma. This edema is characterized by asthmatic-type rales in the lungs. An associated bronchospasm with this clinical syndrome has been found by Heyer and Plotz. The most severe form of edema is clinically recognized as acute pulmonary edema. (Figs. 1 to 4.)

Pulmonary edema may begin gradually or suddenly. The patient may complain of oppression or pain in his chest and will be apprehensive. Respiratory distress varies from dyspnea to orthopnea. The patient will expectorate frothy and perhaps blood-tinged sputum in large amounts. He will be sweaty, pale and have moist rales throughout his lungs. The pulse rate and blood pressure will be increased in less severe cases but the blood pressure will be decreased in severe cases.

TREATMENT

The appearance of acute pulmonary edema is a very serious complication and carries with it a high mortality rate. Sonne and Hilden reported in forty-two patients with acute pulmonary edema that the systolic blood pressure was above 190 mm. of mercury in 73 per cent. In this group three patients died. In 23 per cent of the cases the blood pressure was under 90 mm. of mercury systolic, and in this group three of four patients died. Since pul-

monary edema is such a serious complication, every effort should be made to prevent its occurrence. Before surgery the patient should be examined to note whether a condition exists which predisposes toward pulmonary edema. The edematous patient should be rid of his edema. Serum proteins, serum electrolytes and hematocrit should be normal. Digitalization should be used when needed.

During the operation and in the convalescent period a clear airway must be maintained. Good intratracheal anesthesia, proper aspiration and an effective cough are most important. Bronchoscopy and less often tracheotomy may be necessary. The lungs must be kept expanded and atelectasis and pneumonia prevented. Postoperatively the patient should turn hourly, and deep breathing and early mobilization should be encouraged.

A high concentration of oxygen should be used during the operation with sufficient tidal volume to wash out the carbon dioxide. To prevent cardiac arrest anesthesia should be avoided. Oxygen should be administered postoperatively.

The blood lost during the operation or in the postoperative period should be replaced cubic centimeter for cubic centimeter as the blood is lost. If an increased blood volume already exists (as in mitral stenosis) or pulmonary edema is anticipated, the patient will benefit from a blood loss up to 500 cc. The patient should never receive more blood than he has lost. A damaged heart tolerates an excess of blood very poorly and serious damage may result from a 500 to 1,000 cc. overtransfusion. If a patient with an increased blood volume is also anemic, it is preferable to give the patient red blood cells without plasma.

Intravenous fluids should be administered with caution during surgery and in the postoperative period. In general, sufficient saline solution should be given to replace the saline lost. Usually salt is retained in the body in the first few days postoperatively so that 500 cc. of isotonic saline per twenty-four-hour period should not be exceeded. The serum electrolytes and urinary chloride can be measured to estimate the need for sodium chloride. If a surgeon restricts saline infusions, he must also be careful not to administer excess glucose solutions intravenously. If a patient on a restricted sodium chloride intake receives relatively large amounts of parenteral glucose solutions, the total body water may be increased causing a relatively low sodium concentration. This condition (water intoxication, hyponatremia) may have serious results if not recognized and treated. It will usually be necessary to administer concentrated sodium chloride. In the patient prone to develop pulmonary edema this sequence of events will not be beneficial, and it would have been better to re-establish early administration of oral fluids.

If pulmonary edema is feared, it is best to elevate the head of the patient as soon as possible. This tends to lower the venous return to the right heart and to decrease the output of the right ventricle.

If acute pulmonary edema occurs, prompt treatment is essential. The head of the patient should be elevated to reduce the venous return to the heart. Intermittent tourniquets to the extremities help trap blood in the extremities, further decreasing the effect of blood volume and venous return to the heart. The tourniquets will produce anoxia in the extremity whereby serum will leak from the capillaries and further decrease the defective blood volume. A phlebotomy of 500 cc. of blood may be life-saving. Aminophylline is thought to have a direct relaxant effect on the veins which may help diminish the venous return. If the patient is not digitalized, an intravenous digitalis preparation should be given. Morphine, 10 mg., should be administered unless there are specific contraindications. Morphine will allay the anxiety of a patient and has additional beneficial effects in pulmonary edema not well understood. Churchill and Cope found that lungs engorged with blood produced a reflex rise in respiratory rate. It is thought that morphine may have a depressant effect upon the reflexly induced dyspnea.

Anoxia must be strenuously treated. A snug-fitting face mask should be used with an adequate flow of oxygen. Altschule has criticized the use of 100 per cent oxygen, and recommended instead a mask or nasal catheter with an oxygen flow of about 6 L. per minute yielding concentrations of 40 to 80 per cent. A mask which permits the patient to exhale against an adjustable positive pressure may be helpful at times. A positive pressure should start at plus 2 to plus 5 cm. of water and the pressure should be lowered 1 cm. every one to four hours dependent upon the condition of the patient.

Excessive positive pressure will interfere with the circulation of the blood through the lung and thus lower the cardiac output.

A clear airway must be maintained; cough and aspiration usually suffice. In the unconscious patient with a central nervous system injury tracheotomy may be indicated. Foaming of the edema fluid in the airway markedly aggravates the respiratory disease. Luisada recommended the use of an antifoaming agent and found that vaporized ethyl alcohol was the most beneficial. This can be administered by pumping the oxygen source through an ethyl alcohol vaporizer. The beneficial effects may be very dramatic.

The aforementioned measures should be promptly instituted for acute pulmonary edema. Certain additional measures should be instituted to prevent recurrence of the edema. The daily sodium chloride intake should be restricted to as low as 200 mg. Mercurial diuretics can be used to increase the sodium chloride excretion but care must be taken not to produce hyponatremia. Ion exchange resins can be used to remove sodium from the gastrointestinal tract. If pleural fluid is interferring with respiration, it should be aspirated. It may be necessary to aspirate fluid from the peritoneal cavity. The intake of salt-free fluid orally need not be restricted if proper restriction of the daily sodium chloride intake is maintained.

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Pulmonary Hemorrhage

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PULMONARY hemorrhage in the sense in which it is used in this discussion may be defined as hemoptysis originating in the lower respiratory tract, which consists of the pulmonary parenchyma, the bronchi and trachea. Hemoptysis is defined as the expectoration of blood, regardless of its source. Since a patient presenting the complaint of expectoration of blood is usually ignorant of the source of the blood, it is desirable to consider all causes of hemoptysis in a discussion of the subject of pulmonary hemorrhage. A knowledge of all causes is essential in order to determine whether or not the source of bleeding is actually in the lower respiratory tract.

Injury or disease of any structure communicating with the naso-oro-pharynx and the tracheobronchial tree must be considered in the differential diagnosis of hemoptysis. Even the possibility of hematemesis must be kept in mind. The patient may be unable to state whether the blood appeared following a cough, vomiting or a clearing of the nose to aspirate any discharge from the nasopharynx. Sometimes there is no act such as coughing associated with the appearance of the blood. The patient may state that there is merely a sensation of something in the throat, and a simple clearing of it produces the blood.

According to most writers the most frequent causes of hemoptysis are tuberculosis, bronchiectasis, carcinoma, pulmonary abscess and mitral stenosis.[1,2] However, there are many other causes and the unusual must always be kept in mind. We have seen hemoptysis due to hemorrhage from Wharton's duct in the presence of a stone with no symptoms whatever other than the expectoration of the blood. We have also seen hemoptysis from carcinoma of the nasopharynx, which defied detection even after many examinations by nasopharyngoscopy.

A partial list of the causes of hemoptysis, in addition to injuries, may be given best through a classification of pulmonary diseases as presented by King.[3] (Table 1.)

This classification represents a fairly complete list of pulmonary diseases, but it does not include such diseases as aortic aneurysm or diseases of the esophagus or other structures in the mediastinum which give rise to secondary pulmonary or tracheobronchial disease that may be associated with hemoptysis. It does not include pulmonary vascular diseases, such as arterial aneurysm and arteriovenous fistula. Neither does it include the presence of foreign bodies in the tracheobronchial tree or lung, or blood dyscrasias.

TABLE 1

- A. Infections
  - 1. Tuberculosis
  - 2. Other bacterial
    - Pyogenic, brucellosis and tularemia
  - 3. Mycotic
    - Actinomycosis
    - Blastomycosis
    - Coccidioidomycosis and others
  - 4. Rickettsial
  - 5. Virus
  - 6. Parasitic
- B. Inhalations
  - 1. Industrial
    - Silicosis and others
  - 2. Other
    - Vomitus and lipiodol
  - 3. Thermal
- C. Neoplasms
  - 1. Primary
  - 2. Secondary
  - 3. Generalized
- D. Blood diseases
  - 1. Leukemia
  - 2. Polycythemia
  - 3. Sickle cell anemia
- E. Generalized diseases
  - 1. Sarcoidosis
  - 2. Loeffler's syndrome
  - 3. Rheumatic fever and others
- F. Fibrosis
- G. Granulomatosis
- H. Bronchiolectasis
- I. Circulatory disturbances
  - 1. Pulmonary edema
  - 2. Hemosiderosis
  - 3. Emboli and infarcts

There are many examinations available at the present time, the use of several of which usually suffice to establish the diagnosis. While a complete history and complete physical examination are absolutely essential in the study of every patient, usually one can reach only a tentative diagnosis after their use. Nearly always additional examinations are indicated and necessary. A complete list of the diagnostic procedures available is shown in Table II.

TABLE II
DIAGNOSTIC PROCEDURES

1. Routine history and physical examination
2. Routine laboratory studies (blood and urine)
3. Sputum studies:
   - Character and amount
   - Smears and cultures
   - Cytologic examinations
4. Gastric washings (if no satisfactory sputum available)
   - Smears and cultures
5. Fluoroscopy of the chest
6. Roentgenograms of the chest in more than one projection
7. Tuberculin and other skin tests
8. Bronchoscopy
9. Bronchography
10. Rhinoscopy, nasopharyngoscopy, laryngoscopy
11. Barium swallow, upper gastro-intestinal series, barium enema
12. Pleural fluid studies:
    - Character and amount
    - Bacteriologic examinations
    - Cytologic examinations
13. Biopsy of lymph nodes
14. Biopsy of pleura
15. Biopsy of lung
16. Angiocardiography and direct angiography (aortography)
17. Cardiac catheterization
18. Artificial pneumothorax and pneumoperitoneum
19. Exploratory thoracotomy

Many of the examinations enumerated are necessary in any given case to ascertain the cause of hemoptysis. However, it is to be noted that the most basic, which are also the simplest for the patient, do not require hospitalization. These consist of the history and physical examination, the sputum and roentgenographic examinations and the cutaneous tests.

When available, examination of the sputum by proper methods and on repeated occasions is of the utmost importance. This applies particularly to the diagnosis of fungous, tuberculous and neoplastic disease. It is possible to establish the unequivocal diagnosis of fungous and tuberculous disease only by bacteriologic methods. In recent years it has become possible to establish the diagnosis of carcinoma of the lung by the cytologic method in a high percentage of the cases[4] in which other methods short of exploratory operation and tissue biopsy have failed.

It is well to remember that normal roentgenograms of the chest do not exclude the presence of intrathoracic disease. Often the diagnosis of bronchiectasis cannot even be suspected from a study of plain films alone. Bronchography is essential to determine the presence or absence of bronchiectasis, or bronchiolectasis. There are also instances of normal roentgenograms occurring in cases with proven carcinoma of a bronchus. The neoplasm may not be apparent on a plain x-ray film, unless it produces a high degree of obstruction of a bronchus. In these cases one may actually not see the tumor on the x-ray films but rather the evidence of infection, atelectasis or, more rarely, obstructive emphysema beyond the obstructed bronchus.

There are observations made on fluoroscopy of the chest which may not be made on roentgenographic studies of the chest alone. Of course, these concern the motion of the bony thoracic cage, the diaphragms, the structures in the mediastinum and changes in the degree of aeration of the lungs. An attempt to make comparable observations may be made by a study of roentgenographic films made in inspiration and expiration, but these should not replace fluoroscopy as a most important method of study.

The extreme importance of bronchoscopy in the search for the cause of hemoptysis should be well recognized. Bronchography is also necessary in most, but not all cases.

In cases in which the cause of hemoptysis is at all obscure, careful and often repeated endoscopic examinations of the upper respiratory tract are indicated.

The roentgenographic studies of the alimentary tract are always indicated when the cause of hemoptysis is obscure, when the roentgenograms of the chest are normal, or when the possibility of a primary extrathoracic malignant tumor exists. Biopsy of readily accessible and often enlarged cervical and axillary lymph nodes is a most valuable procedure. In selected cases biopsy of enlarged mediastinal lymph nodes should be used more often than it is; when roentgenograms of the chest are normal

except for evidence of mediastinal lymphadenopathy and when all other non-operative diagnostic procedures which are indicated are non-contributory or non-diagnostic.

Adequate and repeated studies of any pleural fluid present are essential. Biopsy of the pleura is a simple procedure when the pleural cavity is already obliterated at the site of the operation. It may be performed under local anesthesia, without resection of a segment of rib. In the occasional case it may be the only method by which the correct diagnosis may be established.

Biopsy of the lung by needle aspiration is not recommended generally. It is used only in cases of obviously inoperable carcinoma in which the tissue diagnosis cannot be established otherwise. Biopsy of the lung by open thoracotomy is referred to later as exploratory thoracotomy.

Roentgenographic studies of the vascular system have become essential in selected cases. These are made by the injection of contrast media, either intravenously or intra-arterially, by needle or by catheter. Artificial pneumothorax and artificial pneumoperitoneum as diagnostic procedures are more of historical interest than of practical value today.

In an occasional case the pulmonary arterial pressure must be determined by cardiac catheterization. The presence or absence of pulmonary hypertension may be a key observation in the consideration of the possibility of the existence of mitral valvular disease.

Exploratory thoracotomy has become a diagnostic procedure of the utmost importance. It is indicated in cases of possible unilateral intrathoracic neoplasm, especially carcinoma, with or without hemoptysis, in which all non-operative and other lesser diagnostic procedures have been utilized to no avail.

The treatment of pulmonary hemorrhage should be directed toward the cause. Most often no urgent or immediate treatment is necessary because the bleeding is either never alarming or it ceases spontaneously. In other cases usually all that is necessary is the allaying of anxiety and apprehension by the administration of narcotics, provided the dosage administered does not lower the normal respiratory rate or depress the cough reflex. In cases of severe hemorrhage from the lung, if the proper side can be determined, artificial pneumothorax may be tried. It is believed that it is rarely effective because the degree of collapse of the lung effected is not necessarily associated with decreased pulmonary blood flow, and because the presence of overlying pleural adhesions frequently prevents satisfactory collapse of that portion of the lung in which the hemorrhage is originating. Fortunately, even massive pulmonary hemorrhage is rarely fatal, except in cases of very extensive injury or disease.

The prognosis in cases of hemoptysis, whether slight or massive, varies with that of the disease found to be the cause. In many cases, however, no cause can be found. Probably the number of cases with idiopathic hemoptysis is about 10 per cent.[2,5] These deserve extremely careful observation over a period of years. Active pulmonary tuberculosis will develop in an occasional case. Probably others have bronchiectasis. Fortunately, most seem to have no recurrence of the hemoptysis,[6] thus allowing the diagnosis of probable non-specific bronchitis to be made by the process of exclusion.

SUMMARY

A brief discussion of pulmonary hemorrhage is presented. In particular the possible etiologic factors and the diagnostic technic available for the study of such cases are reviewed.

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Segmental Bronchi and the Bronchopulmonary Segments

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THE concept of the bronchopulmonary segment may be said to date from the writings of Ewart,[1] whose classic treatise on the bronchi and pulmonary vessels was published in London in 1889. However, little attention was paid to this concept and little or no clinical use made of it until the paper of Kramer and Glass,[2] presented before the American Broncho-Esophagological Association in 1932. This paper was a combined bronchoscopic and surgical study dealing with the diagnosis, localization and external drainage of pulmonary abscess. The authors sought to "establish a smaller and more accurate unit of localization than the lobe" and they described the bronchopulmonary segment as not only an anatomic but also a pathologic unit, pointing out the importance of identification of the various segmental orifices and knowledge of the size, shape and topographic position of the outer surface of each associated segment on the chest wall. In an anatomic study of eighty pairs of human lungs they found the lobar and segmental branches to be constant in 85 per cent of the cases and they named these segments and their corresponding bronchi, using a simple nomenclature based on their position in the lung. Furthermore, with specific relation to the problem of pulmonary abscess, they found that practically all abscesses have a definite position in one of the bronchopulmonary segments, and they emphasized the fact that the bronchoscopist holds the "key position" for information concerning bronchopulmonary suppurative disease. Two years later (in 1934) a paper by Nelson[3] appeared, likewise calling attention to the importance of the study of bronchial anatomy in the management of pulmonary abscess, but particularly with respect to position for postural drainage. He pointed out the advantage of continuous postural drainage in a correct position over intermittent postural drainage of the kind generally practiced without regard to the anatomic direction of the bronchus draining the abscess or the location of its orifice in relation to other orifices. He stated that postural drainage attempted without consideration of these facts was not only valueless but also dangerous. Hardie Neil[4–6] has contributed a number of valuable papers on this subject, the first published in 1936. He brought to bear a large experience in comparative as well as human anatomy and a keen clinical sense. One of his outstanding contributions was a composite perimetric perspective diagram representing the position and relations of various segmental orifices as seen by the bronchoscopist. In a paper read in 1942 and published the following year Jackson and Huber[7] reiterated what others had said concerning the importance of the study of applied anatomy of the bronchi and lungs, and particularly the significance of the concept of the bronchopulmonary segment. They suggested that the lungs be thought of as subdivided according to bronchial distribution rather than according to fissures, because the former are more constant and because this concept affords a more sound basis for understanding the physiology and pathology of the bronchi and lungs. After prolonged laboratory and clinical studies they reviewed all the systems of nomenclature suggested by the numerous authors who had by that time contributed to this subject. They decided to work out a new terminology because none of those previously suggested satisfied them. They sought "a standard clinical terminology which will be acceptable to

the bronchologist, the thoracic surgeon, and the radiologist, and which will meet with the approval of the anatomist." The nomenclature suggested by Jackson and Huber was as follows:

Lobes		Segments
Upper		Apical
		Posterior
		Anterior
Middle		Lateral
		Medial
Lower		Superior
		Medial basal
		Anterior basal
		Lateral basal
		Posterior basal
Upper	Upper Division	Apical-posterior
		Anterior
	Lower Division (Lingular)	Superior
		Inferior
Lower		Superior
		Anterior basal
		Lateral basal
		Posterior basal

This nomenclature (Fig. 1) has met with unexpectedly wide acceptance by anatomists[8,9] and clinicians of various specialties.[10–12] Some of the comments concerning it are quoted in a Report of the Committee on Nomenclature of the American Broncho-Esophagological Association and published in its Transactions.[13] Gray's standard textbook of anatomy[14] has adopted the terminology for its current (25th) edition. At the New Orleans meeting of the American Association for Thoracic Surgery in 1948 this terminology was officially approved.

In 1949 an international committee met in London at the invitation of Mr. Victor Negus, President of the Fourth International Congress of Otolaryngology, and this committee, after several hours of deliberation, decided upon a terminology almost identical with that of Jackson and Huber, though differing in the preference for the old term "apical" of the lower lobe for the segment called "superior" by Jackson and Huber. This was really the only important difference. The report of the aforementioned committee was carefully prepared by Brock.[15] The nomenclature suggested by this committee has still not been adopted in the United States, nor has it been adopted universally elsewhere, although the Thoracic Society (British) of course adopted it. Boyden[16] advises that we "hold to the Jackson-Huber terminology until such a time as "an official international committee can deal with these problems." Boyden particularly prefers the terms "superior" and "subsuperior" for the upper segments of the lower lobe.

Nomenclature is important and the general adoption of one set of names would certainly lead to better understanding of the literature, but even more important is the anatomic concept itself. To the bronchoscopist the concept of the bronchopulmonary segment is important in two ways: first, a knowledge of the topographic anatomy enables him to tell from the roentgenograms, and particularly from the lateral projections, how to chart his course in the bronchoscopic approach to a lesion or a foreign body; second, such knowledge enables him, when he looks through the bronchoscope, to interpret the endoscopic findings intelligently, since he will know when he looks at a certain branch bronchial orifice just what direction its bronchus takes, and what the size, shape and relations of its tributary segments are. Furthermore he will be able to report his findings in such a way as to be of maximum value to the referring physician or surgeon, and to fit in with the reports of the other clinicians and the radiologist.

The clinical importance of bronchopulmonary anatomy, and particularly the segmental concept, might be summarized as follows: (1) In abscess (Fig. 2) such study facilitates both external surgical drainage and postural drainage, as well as endoscopic drainage and the endobronchial instillation, by means of a catheter or bronchoscope, of penicillin or other drugs as described by Métras.[17] (2) Bronchiectasis is, as emphasized by Overholt,[10] "a segmental disease," and segmental resection is the order of the day especially in bilateral cases. Economic resection of only the diseased segments (after careful complete mapping of all segments of both lungs) can often be carried out in patients who would have been considered inoperable a few years ago. In 60 per cent of the cases of left lower lobe bronchiectasis the adjacent segment of the upper lobe must be removed along with the lower, if the patient is to be cured. (Fig. 3.) (3) In tumors early diagnosis may often be made by bronchoscopy when the lesion is segmental, causing only a segmental atelectasis; and although cure may require removal of the entire lobe or even the lung if the tumor is malignant, there will be a better prospect of cure than if diagnosis is not made until the whole lobe or the whole

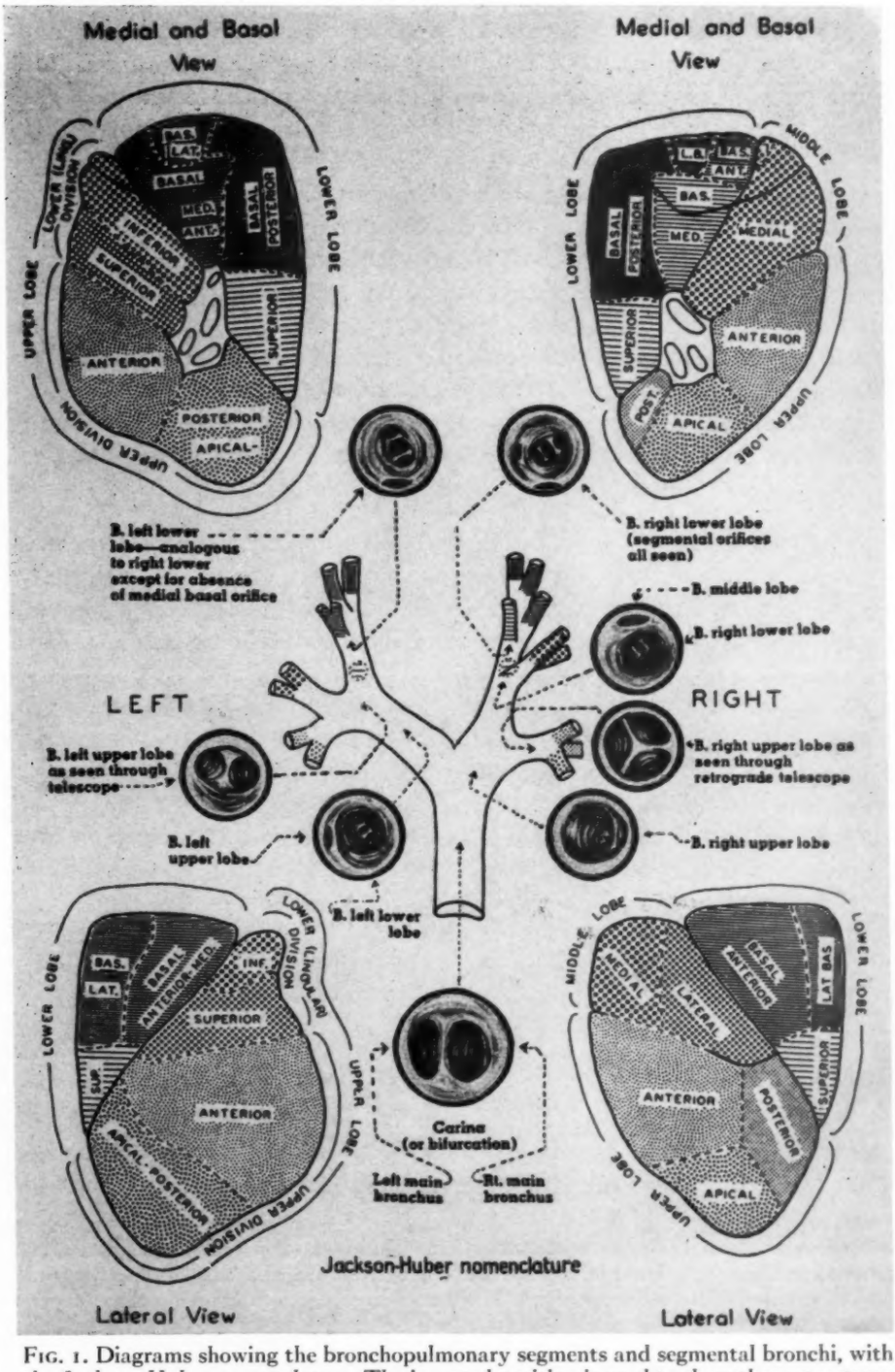

FIG. 1. Diagrams showing the bronchopulmonary segments and segmental bronchi, with the Jackson-Huber nomenclature. The inverted position is used to show these structures in the same relation as the bronchi and lungs of a patient on the bronchoscopic table during bronchoscopy. (From JACKSON and JACKSON, Bronchoesophagology. Philadelphia, 1950. W. B. Saunders Co.)

lung is atelectatic. As Foster-Carter[18] has well stated, "perhaps the most important contribution to diagnosis is that recognition of a segmental lesion directs attention to the condition of the related bronchus." (4) In tuberculosis the sites of predilection are found to be not the apical but the posterior (or "subapical") segment of the upper lobe and the supe-

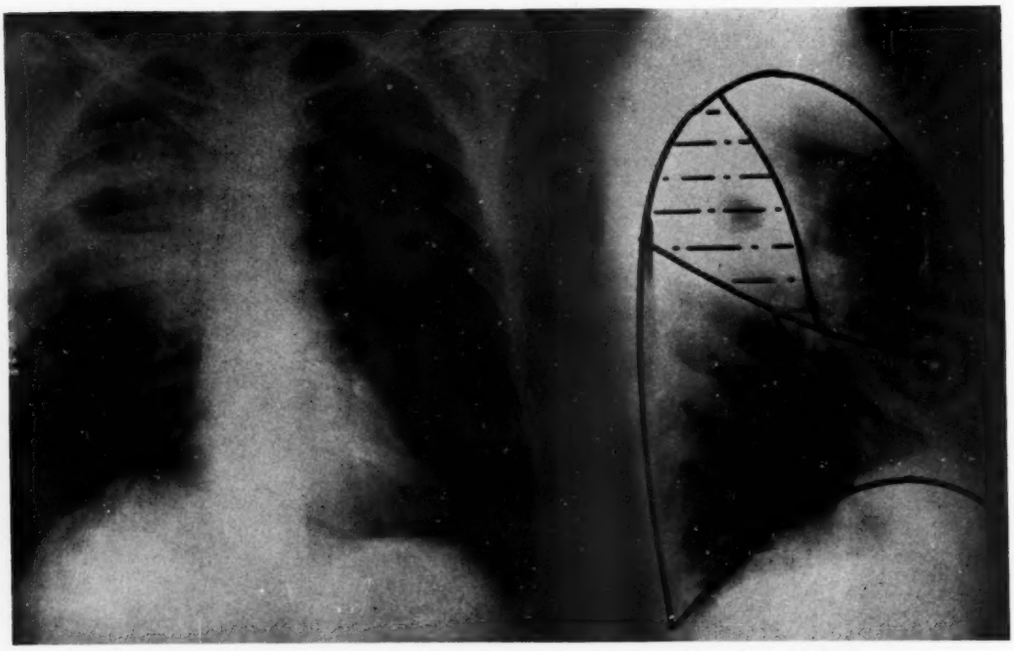

FIG. 2. Abscess of the posterior segment of the upper lobe of the right lung.

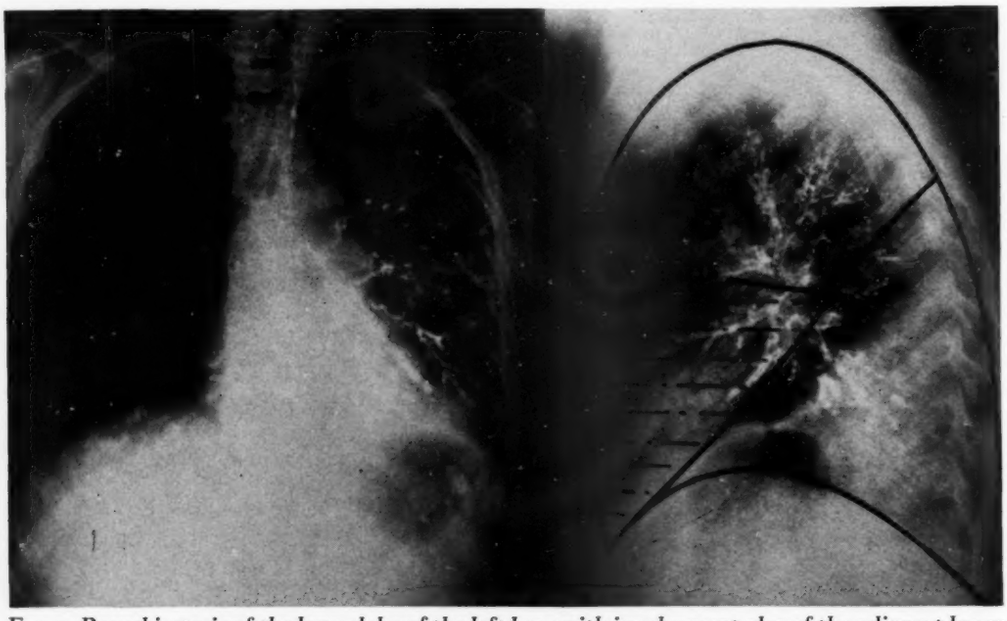

FIG. 3. Bronchiectasis of the lower lobe of the left lung with involvement also of the adjacent lower (or lingular) division of the left upper lobe. This association is seen in approximately 60 per cent of the cases.

rior (or "apical") segment of the lower. Much light has been thrown on the pathogenesis of tuberculosis by the application of modern anatomic concepts to the study of the disease, which, as pointed out by the distinguished Spanish phthisiologist, Sayé,[19] should be thought of as a "tracheobronchopulmonary" disease. (5) In foreign body a knowledge of the segmental anatomy is of vital importance, and no case of foreign body in the air passages should be attempted without accurate lobar and segmental localization, using anteroposterior and lateral, and if necessary, oblique roentgenograms. Such study has, for example, explained the mysterious inability to contact a foreign body seemingly easy to reach by show-

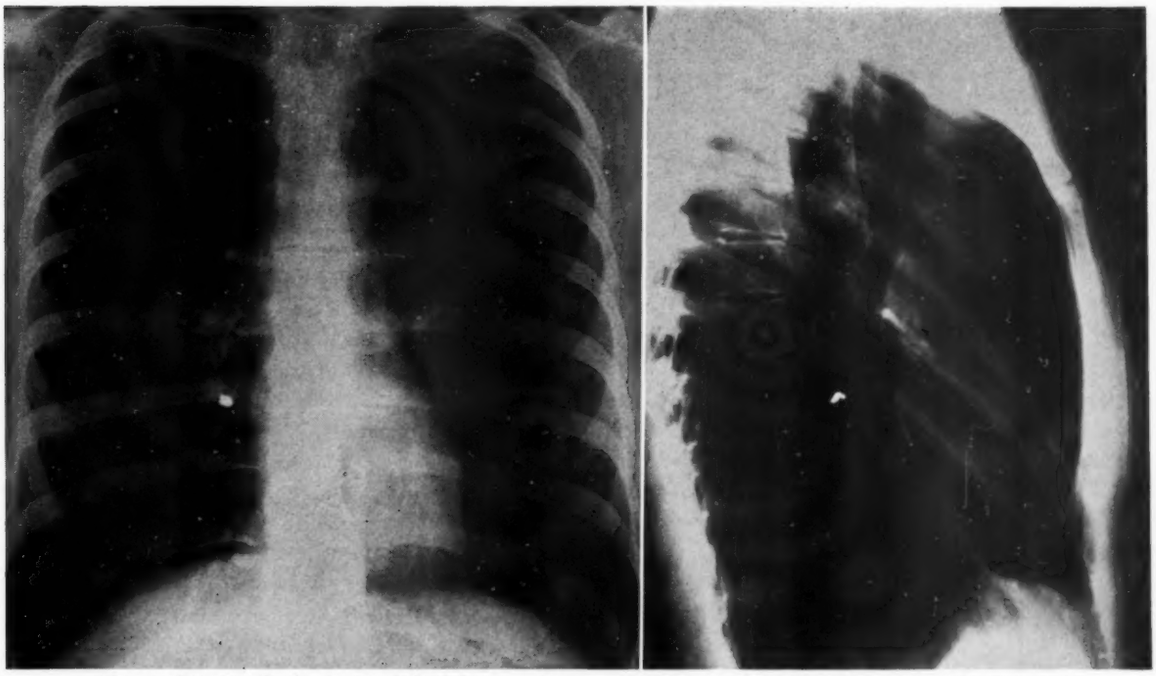

FIG. 4. Foreign body (tooth inlay) in superior segmental branch of right lower lobe bronchus.

ing that instead of being in the main bronchus as it appeared to be in the anteroposterior film, the foreign body was really in a segmental branch. (Fig. 4.)

In view of the aforementioned facts it can be stated without hesitation that the concept of the bronchopulmonary segment, based upon the subdivision of the lung according to bronchial distribution, is one of the most important practical principles in the present day diagnosis and treatment of bronchopulmonary disease.

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Segmental Localization of Pulmonary Disease

MEDICAL AND SURGICAL SIGNIFICANCE

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THE remarkable progress of thoracic surgery in the past two decades illustrates the advantage of coordinated medical effort. The anesthetist, the physiologist, the anatomist, the bronchoscopist and the radiologist have each made important contributions to this advancement. There is no better example of such combined study than that of the "bronchopulmonary segments."

Although the sublobar divisions of the lung had been described a half century earlier,[6] it was not until a bronchoscopist and a surgeon became interested in the localization of abscesses[12] that clinical attention was directed to these lung units. With the increasing skill of the surgeon in resecting small portions of lung[4,5] conserving tissue and function, came the greatest incentive to further anatomic studies of the sublobar segments[2,3] and their radiographic localization.[7,10,17]

The term bronchopulmonary segment could be applied to any unit of lung and its draining bronchus, but through usage it has come to designate that portion which is aerated by a tertiary bronchus. In recent years the terminology applied to these lung units has been simplified and standardized,[9] thus eliminating a serious source of confusion.

The chart shown in Figure 1 outlines the radiographic density of each lobe and segment as it would appear if involved by a consolidating process. It should be understood that the x-ray shadow of a bronchopulmonary segment cannot be correlated with its surface anatomy alone since it represents the sum of its three-dimensional density. The reference numbers designating each of the segments and their corresponding bronchi (Fig. 2) indicate the order in which they arise from the lobar bronchi.

When localizing lesions with the aid of this chart, consideration must be given to the normal variation in size of the segments and especially to such complicating influences as atelectasis, fibrosis and emphysema. In localizing disease which involves part of or more than one segment, it is also necessary to consider the varying extent to which the adjoining segments overlap each other.

In addition to recognizing the common lobes which are subdivided into pulmonary segments, it is well to be familiar with the accessory lobes which may be encountered. Although the writer has seen one pair of lungs which were divided into eleven clearly defined lobes with fully developed pleural fissures, it is more frequent to find that even the five which are commonly described are not always separated by a fissure.

The accessory lobes shown in Figure 3 are those which can often be recognized by the presence of some degree of fissure formation. Two of these accessory lobes (*b* and *c*) incorporate individual lung segments. The third (*a*) includes a variable portion of the upper lobe and occurs only on the right side.

The azygos lobe (*a*, Fig. 3) derives its name from the fact that its separating fissure results from a developmental aberrance in the course of the azygos vein with a consequent infolding of parietal and visceral pleura. This lobe is seen on about 1 per cent of chest roentgenograms and is recognized by the lateral convexity of its fissure and the visibility of the azygos vein. The latter is frequently misplaced due to embryologic arrest in its descent.

The accessory lobe designated as *b* in Figure 3 was first described by Dévé in 1900.[2] It represents a subdivision of the lower lobe by a horizontal fissure. This occurs more frequently in the right lung than in the left and may appear on a level with, but posterior to, the familiar horizontal fissure which separates the right upper lobe from the right middle lobe. The posterior horizontal fissure of Dévé occurs as a fully developed pleural fold in about 5 per cent of lungs and as a partially developed fissure in about 22 per cent.[2] This accessory lobe includes the apical (superior) segment.

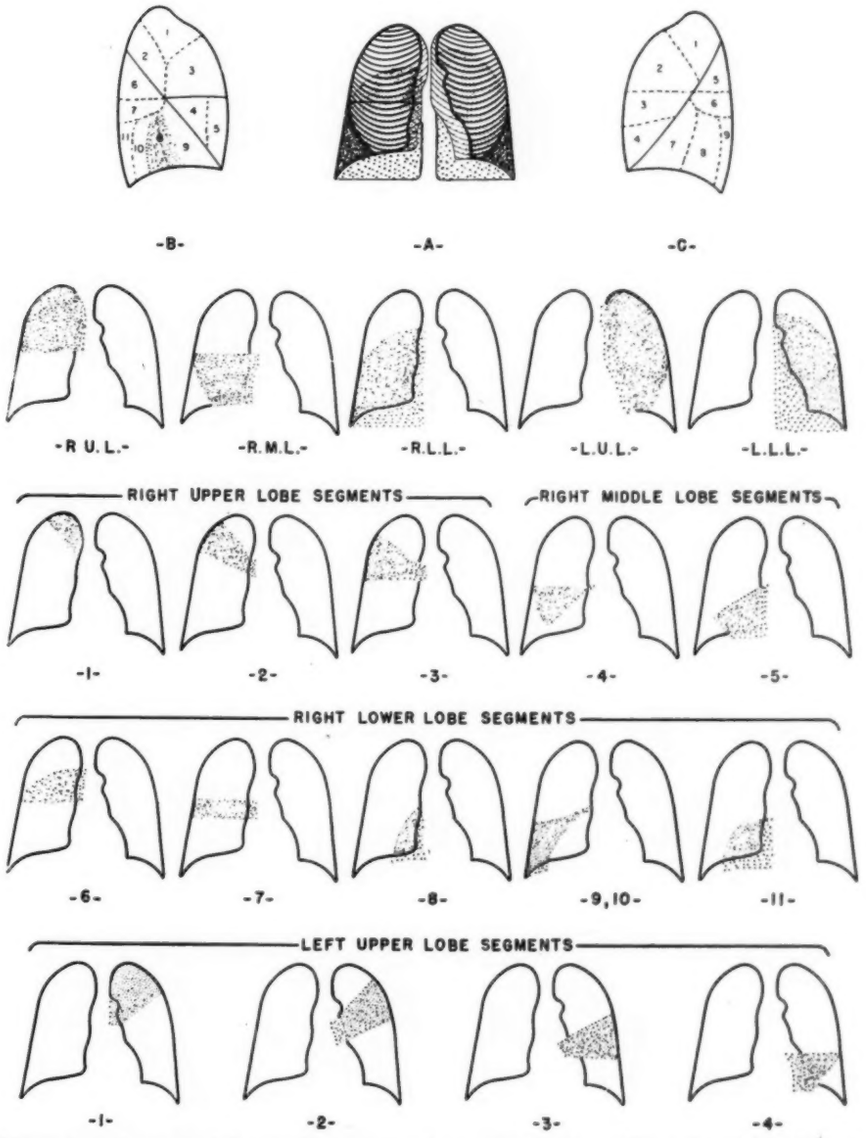


FIG. 1. Chart of bronchopulmonary lobes and segments. A, composite three-dimensional drawing of the five lobes of the lung showing the degree to which they overlap and their relation to the cardiovascular silhouette. The upper and middle lobes on the right as well as the upper lobe and its lingula on the left are contoured for transparency, whereas the lower lobes are stippled. B, lateral view of right lung showing the relation of its three lobes as outlined by continuous lines and its bronchopulmonary segments as outlined by interrupted lines. C, lateral view of left lung showing its two lobes and their segments. The segments of the left lower lobe have not been included in the drawings since their appearance and location resemble those of the right lower lobe except for absence of a distinct median basal segment. The difference in number of segments in the right and left lung as seen on lateral drawings A and B is accounted for by combination of apical and posterior segments in the left upper lobe and absence of the median basal segment in the left lower lobe. (See corresponding bronchi in Figure 2.) *Right upper lobe segments* (*R.U.L.*). (1) apical, (2) posterior, (3) anterior. *Left upper lobe segments* (*L.U.L.*): (1) apical-posterior, (2) anterior. *Right middle lobe segments* (*R.M.L.*): (4) lateral, (5) medial. *Lingula segments of L.U.L.*: (3) superior, (4) inferior. *Right lower lobe* (*R.L.L.*): (6) apical (superior), (7) subapical (50 per cent of cases), (8) median basal, (9) anterior basal, (10) lateral basal, (11) posterior basal. *Left lower lobe* (*L.L.L.*): (5) apical (superior), (6) subapical (50 per cent of cases), (7) anterior basal, (8) lateral basal, (9) posterior basal. (This chart, based on another article,[10] is reproduced from the author's manual on "Sectional Radiography of the Chest." New York, 1953, Springer Publishing Co.)

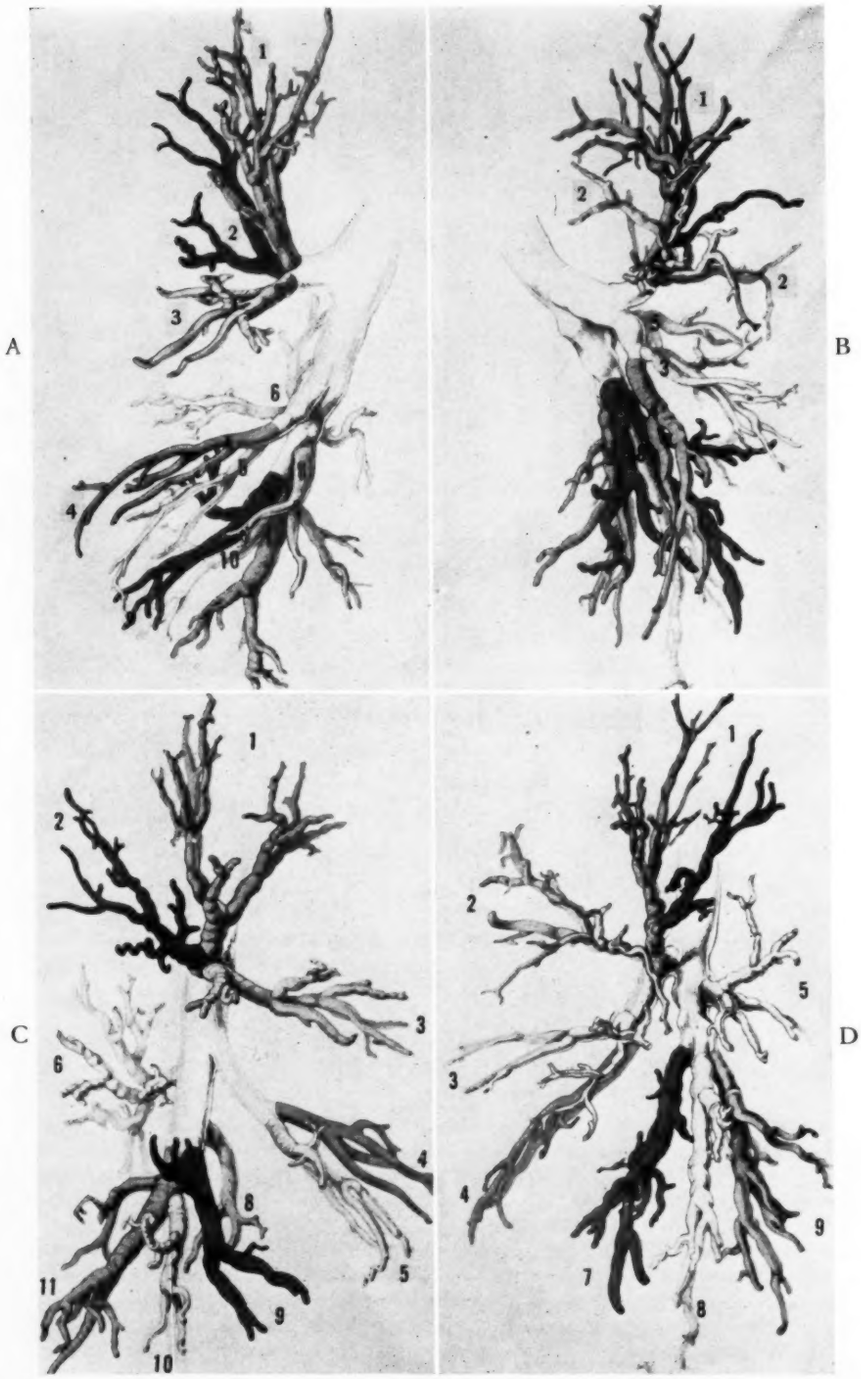


FIG. 2. Lobar and segmental bronchi. A, right lung bronchi, frontal view. B, left lung bronchi, frontal view. C, right lung bronchi, lateral view. D, left lung bronchi, lateral view. Each bronchus is similarly shaded in the frontal and lateral views. The subapical segment bronchi which occur in 50 per cent of lower lobes are not shown in these drawings, thus accounting for the absence of numbers 6 and 7 in the left and right lungs, respectively. *Right upper lobe segments:* (1) apical, (2) posterior, (3) anterior. *Left upper lobe segments:* (1) apical-posterior, (2) anterior. *Right middle lobe segments:* (4) lateral, (5) medial. *Lingula segments of L.U.L.:* (3) superior, (4) inferior. *Right lower lobe segments:* (6) apical (superior), (7) subapical (50 per cent of cases), (8) median basal, (9) anterior basal, (10) lateral basal, (11) posterior basal. *Left lower lobe segments:* (5) apical (superior), (6) subapical (50 per cent of cases), (7) anterior basal, (8) lateral basal, (9) posterior basal. (From BROCK, R. C. Anatomy of the Bronchial Tree. New York, 1947. Oxford University Press.)

The inferior accessory lobe designated as *c* in Figure 3 derives this name from its location. The area included in this lobe corresponds to that of the median basal segment of the right lower lobe. Consequently, when involved by disease its shadow resembles that of the latter segment. The fissure which forms the lateral border of this accessory lobe may be seen to a variable extent in 10 per cent (Rigler) of postero-anterior chest roentgenograms.

The importance of the bronchopulmonary segments may be considered in relation to the pathogenesis, diagnosis and treatment of many lung diseases. With respect to pathogenesis, the distribution of the segments and the direction of their bronchi help to explain the influences of posture and gravity on the aspiration of foreign bodies, the localization of lung abscesses, the effects of bronchial obstruction due to carcinoma, the spread of pulmonary tuberculosis and other bronchogenic processes.

The more or less characteristic segmental localization of tuberculosis and lung abscesses based on the foregoing factors is also an important consideration in the differential diagnosis of chronic pulmonary disease. Thus the common localization of postprimary tuberculosis to the apical and posterior segments of the upper lobes and the apical (superior) segments of the lower lobes is of significance not only diagnostically but also even therapeutically. Similarly, the common sites for localization of lung abscesses have been found in order of frequency to be the posterior and axillary subdivisions of the upper lobe especially on the right and the apical (superior) and posterior basal segments of the lower lobes.[3] In conjunction with a characteristic history or background for aspiration, the presence of poor oral hygiene and/or the appearance of foul sputum, such segmental localizations tend to support the diagnosis of lung abscess. However, it must be stressed, as with all generalities in medicine, that strict reliance on the foregoing characteristics of localization will occasionally lead to serious diagnostic error and is therefore not advisable. Some variation in these patterns of localization is inevitable, based as they are on anatomic factors, on differences in individual postural habits and on postural circumstances during sleep and other states of unconsciousness.

In bronchiectasis the area of lung which should be resected can be determined accurately only by complete bronchographic survey. The careful interpretation of lateral bronchograms as well as the other views presupposes thorough knowledge of the bronchopulmonary segments and their alterations by disease. To assist in identification of the segmental bronchi and in localization of their diseases the

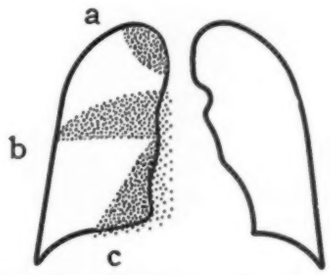
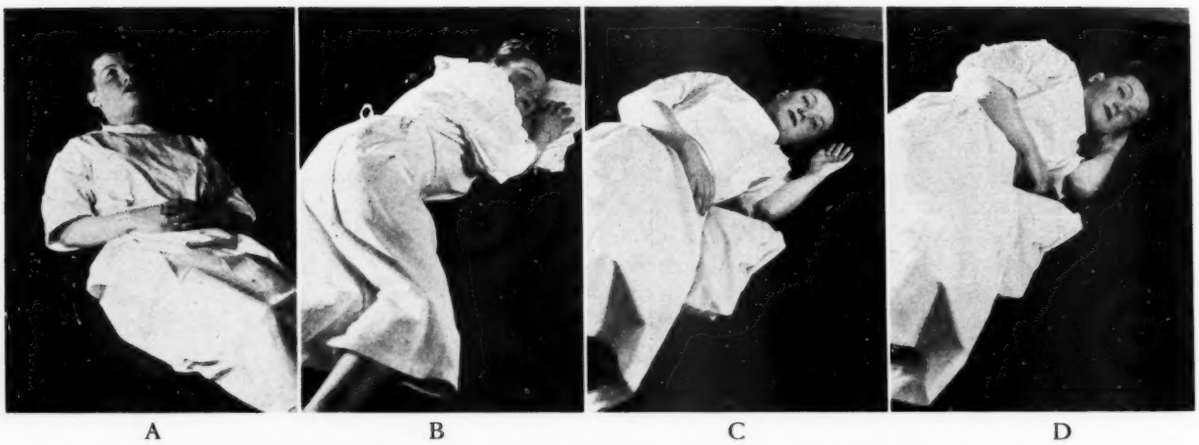


FIG. 3. Three of the more common accessory lobes. (*a*) Azygos lobe, (*b*) Dévé's lobe, (*c*) inferior accessory lobe.

illustrations in Figure 2 have been reproduced from Brock's excellent monograph.[3] The superimposition of bronchi in the frontal views may be seen to preclude their accurate identification. However, the degree to which they are separated on the lateral views makes this the most valuable for bronchographic localization. The oblique views which are not presented here may serve as a useful supplement in some instances.

The importance of segmental localization in the treatment of pulmonary disease may be considered from both the surgical and the medical viewpoint, although in actual practice these are inseparable. To the surgeon such localization offers the opportunity of selecting the most suitable approach for each resection. Whether it be tuberculosis, bronchiectasis or a chronic abscess, accurate localization permits him to conserve pulmonary tissue and function without the risk of overlooking significant disease. For such purposes the method of segmental localization may vary, including in some instances planigraphy, and in other instances bronchography.

From the viewpoint of medical therapy segmental localization makes it possible to apply the influences of gravity to bronchopulmonary drainage more effectively. The effectiveness of present antibiotics combined with early recognition of suppurative disease has increased the opportunity for successful non-surgical treatment. Toward this end a revision in our concepts of postural drainage has been suggested.[11] The old, widely held concept of inverting the patient



A B C D

E F G

FIG. 4. Positions for segmental postural drainage. It should be noted that a pillow is placed under the hips in each position except A and B. Instead of the pillow, shock blocks placed under the foot of the bed will often prove more convenient, more comfortable and more effective.

BRONCHOPULMONARY SEGMENT AND POSITION FOR ITS DRAINAGE

R.U.L.	*R.M.L.*	*R.L.L.*
apical (A)	lateral (C)	apical (superior) (E)
posterior (B)	median (C)	subapical (E)
anterior (C)		median basal (C)
axillary subsegments (D)		anterior basal (C)
		lateral basal (D)
		posterior basal (E)
L.U.L.	(*Lingula*)	*L.L.L.*
apical posterior (A)	superior (F)	apical (superior) (E)
anterior (F)	inferior (F)	subapical (E)
axillary subsegments (G)		anterior basal (F)
		lateral basal (G)
		posterior basal (E)

A, *upright*, drains apical and posterior segments of R.U.L. and L.U.L. B, *left anterior oblique*, drains posterior segment of R.U.L. more effectively. C, *left recumbent oblique*, drains anterior segments of right lung, i.e., the anterior segment of R.U.L. and the lateral and medial segments of R.M.L. D, *left lateral recumbent*, drains axillary subsegments of R.U.L. and R.L.L. as well as lateral basal segment of R.L.L. E, *prone*, drains posterior segments of R.L.L. and L.L.L., i.e., the apical (superior) segments, subapical segments and posterior basal segments. F, *right recumbent oblique*, drains anterior segments of left lung, i.e., anterior segment of L.U.L. as well as superior and inferior segments of its lingula. G, *right lateral recumbent*, drains axillary subsegments of L.U.L. and L.L.L. as well as lateral basal segment of L.L.L. (From KANE, I. J. Segmental postural drainage in pulmonary disease. *Dis. of Chest*, 23: 418, 1953.)

for a few minutes at a time is of limited value, being in some instances unsound anatomically while in other instances uncomfortable or impractical.

To be most effective any current concept of postural drainage should embody the following five principles: (1) It should be based on accurate segmental localization of the disease and knowledge of the direction of its draining bronchus. (2) It should be coordinated with bronchoscopy to assure patency of the bronchial orifice. (3) It should be employed in conjunction with a bronchodilator such as ephedrine sulfate and an expectorant such as potassium iodide as well as detailed instructions to the patient on deep-breathing exercises and controlled cough. Each of these agents is important in assisting the natural cleansing mechanisms of the bronchial tree. (4) It should be accompanied by administration of the most specific antibiotic available for the particular infection. This should be based if possible on bacterial examinations and drug sensitivity tests. (5) It should be instituted early in the course of the disease and maintained on a round-the-clock basis in order to minimize irreversible lung damage.

The positions indicated in Figure 4 are suggested as suitable for round-the-clock application of segmental postural drainage. These positions represent a modification and simplification of former recommendations.[11] Their selection is based on the direction of the draining segmental bronchi rather than on the surface anatomy or x-ray projection of the diseased segment. The choice of each position is also based on the fact that it imposes a minimum of strain and discomfort on very sick or debilitated patients who may be confined to bed.

The posture recommended for gravitational drainage of each segment is intended to elevate that area of lung and bring its draining bronchus toward a vertical position. In a round-the-clock program of postural drainage an alternate position may be necessary. For such purpose and where individual circumstances preclude use of the recommended position the latter may be varied to any degree which still maintains the necessary gravitational influences. The degree of latitude possible for each segment may be estimated by consulting the drawings in Figure 2. Conversely, it should be clear that all positions which favor the retention of secretion in the draining segmental bronchi must be avoided.

In any program of continuous postural drainage, sudden or profuse expectoration is not to be expected and should therefore not be considered a criterion for its success. There is instead a constant elimination of small quantities of secretion. Furthermore, many people who find it impossible to expectorate their bronchopulmonary secretions continually swallow them. The measurement of such material is therefore not always representative of the quantity drained. Evaluation of success in postural drainage can be based only on decrease in toxicity of the patient, decrease in frequency and severity of his cough, and decrease in the size of the roentgenographic shadow or its fluid level, when such is present.

Segmental postural drainage is indicated not only in the medical treatment of suppurative lung disease but also its preoperative management. For the latter purpose such treatment reduces the chance for spread of infection during the induction of anesthesia or for infection of the pleura during the postoperative period of lung reexpansion. Even with improved anesthetic and surgical technics and the availability of potent antibiotics, no one can deny the advantages of performing elective pulmonary resections in an operative field that is as clean as possible. In the postoperative period following chest or abdominal surgery application of the foregoing principles of segmental postural drainage may assume the nature of prophylaxis or therapy.

SUMMARY

The medical and surgical significance of segmental localization of pulmonary disease has been reviewed. Its importance in consideration of the pathogenesis, diagnosis and treatment of certain diseases has been outlined. Simplified reference charts of the lung segments and their bronchi have been presented as a practical aid to their localization.

On the basis of such localization a revision has been suggested in the old concept of postural drainage. Positions suitable for this purpose have been indicated and a coordinated program of gravitational drainage has been recommended.

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Surgery of the Bronchi and Trachea

EXPERIENCE WITH THE PEDICLED PERICARDIAL FAT GRAFT REINFORCEMENT

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SURGERY of the trachea and bronchi now have an important role in the management of diseases of the respiratory tract. This surgery can be performed with a high degree of success by use of the viable pedicled pericardial fat graft devised by one of us (L. A. B.) in 1949.[1] After a considerable clinical and experimental trial this living graft has proved to be just as effective in securing airtight tracheal or bronchial closure in pulmonary resections as has the abdominal omentum in gastro-intestinal operations. Encouraged by these successes this technic of bronchial reinforcement has been extended to plastic and excisional operations of the trachea and bronchi in order to effect a conservation of lung tissue. During the past five years we have employed viable pedicled pericardial fat graft in 293 cases of bronchial division and closure and in twenty-one cases of plastic or resection operations on the trachea or bronchi. The technics employed and the results obtained in this combined series of 313 cases are reviewed.

DEVELOPMENT OF THE VIABLE PERICARDIAL FAT GRAFT

The presence of the adipose tissue lying over the pericardium has received little attention in anatomy books for this tissue seemed to have no special function or surgical use. If one studies this portion of the mediastinum he will note that the pericardial fat pad or thoracic omentum is most prominent over the apex of the heart which is embraced by finger-like projections. (Fig. 1.) This adipose tissue, which is covered with mediastinal pleura, rests on the pericardium where it can be dissected free without damaging the blood supply. The blood supply comes from the branches of the internal mammary and anastomosing trunks, from the pericardiophrenic and musculophrenic vessels. Our present method of developing the pericardial fat graft is essentially the same as has been previously reported.[1] By preserving the branches of the internal mammary artery the pericardial fat tissue extending down the cardiophrenic angle can be mobilized. The blood supply will be conserved to the tip of this "thoracic omentum" by the anastomosing branches from the musculophrenic and pericardiophrenic arteries. Adipose tissue extending anteriorly toward the midline, beneath the sternum, can be completely mobilized up to the branches of the internal mammary artery since there are no vessels coming from the midline. Alternate methods of developing fat graft reinforcement[1] are found in the pericardial fat tissue extending upward to the superior mediastinum where the blood supply is less constant and less extensive. Also, in cases in which the phrenic nerve is to be sacrificed the adipose tissue accompanying the nerve, although small in amount, has an excellent blood supply from the pericardiophrenic vessel.

In our experience pleura, either free or pedicled, lymph nodes and areolar tissue do not provide satisfactory reinforcement of the bronchial closure. Furthermore, in cases of bronchogenic carcinoma it is important to perform a very thorough resection of mediastinal lymph nodes and areolar tissue from the cervical region down to the diaphragm. This leaves no tissue adjacent to the trachea or bronchial stump for reinforcement. In cases in which partial pericardectomy is necessary to obtain satisfactory ligation of the pulmonary vessels, a huge pericardial defect may be present. Herniation of the heart through this opening has resulted in fatal outcome due to

improper cardiac filling. The sling of the pericardial fat graft may be sewn to the pericardium to prevent cardiac displacement. Care must be taken to mobilize sufficient length of the graft to prevent constriction of the pulmonary vessels. In the case of upper lobe or middle lobe resection it is possible to avoid vascular obstruction by placing the graft posterior to the pulmonary artery.

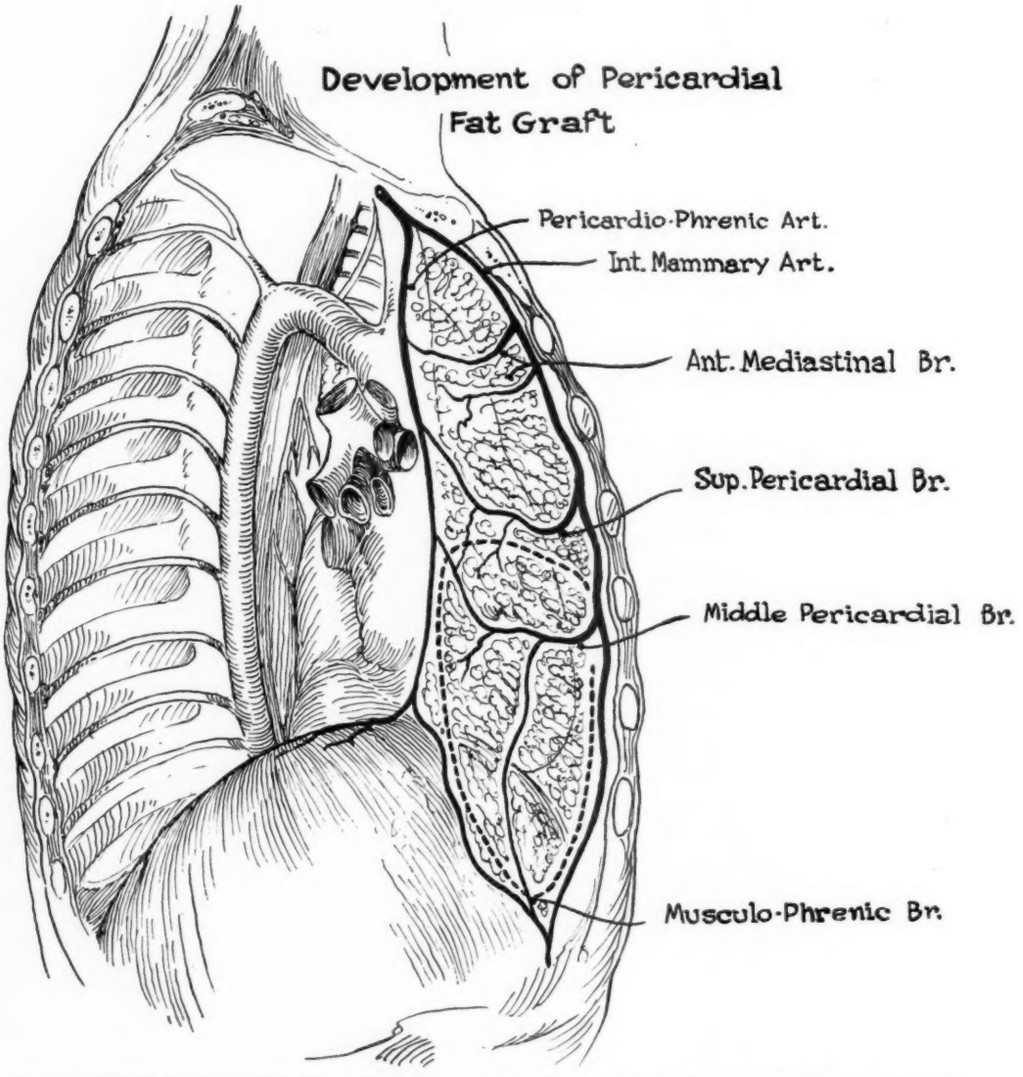

FIG. 1. Pedicled pericardial fat graft is fashioned by dividing branches of musculophrenic and pericardiophrenic vessels. Middle pericardial branch of internal mammary vessels provides adequate blood supply to graft.

BRONCHIAL CLOSURE IN PULMONARY RESECTION

An understanding of the anatomy and function of the bronchi is important in effecting a successful closure of the divided bronchus in pulmonary resection. The bronchi are semi-rigid tubes whose function is to permit the passage of gases in and out of the lungs. The spring-like action of the bronchial cartilage, insuring the patency of the airways, tends to pull apart the sutures used in closing the divided bronchus. This characteristic of the bronchus was not considered important in the early days of mass ligation of the hilar structures. The sloughing of the ligated mass was followed by bronchopleural fistula. Although the first successful lobectomy was performed before the turn of the century,[2] it was not until the individual ligation technic of the vessels

and bronchi was developed for pulmonary resection[3–5] that bronchial closure became a precise surgical technic.

The technic that is most commonly reported today is the division of the bronchus at right angles to the long axis and closure under varying degrees of tension with either interrupted or running sutures. The authors' procedure consists of fashioning an oval-shaped flap of the pliable posterior membranous portion of the bronchus and drawing this up to meet the rigid cartilaginous wall. (Fig. 2.) This insures a closure without tension on the suture line. To avoid trauma to the delicate bronchial mucosa no clamps are used and the bronchial vessels are preserved down to the point of division. The bronchus is then alternately divided and sutured. If excessive secretion is present in the trachea or bronchi, a catheter may be inserted into the open bronchus to directly aspirate this material. Care must be exercised to prevent blood from entering into the bronchus before it is completely closed. In suturing the bronchial stump the stitches should be about 3 mm. deep and the same distance apart. If tied too tightly the sutures may cut through the bronchial wall so that the cut ends of the bronchus are only snugly approximated. For the main bronchi we prefer the 0.007 tantalum wire, which is a strong non-irritating suture. When used with a swaged atraumatic needle only a tiny hole is made in the bronchial wall, approximately the same diameter as the suture material. The cut ends of the wire are turned in to prevent trauma to adjacent vessels. Additional protection to the cut ends of the wire is offered by the pericardial fat graft. For lobar bronchi where the cartilages are smaller, weaker and more irregularly developed, fine silk sutures are most often strong enough. Furthermore, the chance of a wire suture perforating an adjacent pulmonary artery, particularly in upper and middle lobe resections, is obviated. Care must be taken to preserve the bronchial arteries so the blood supply is maintained up to the bronchial stump. Following the closure of the bronchial stump the suture line is tested by covering it with isotonic saline solution. Positive pressure equivalent to that of hard coughing is applied by the anesthetist to the closed intratracheal system. Any leaks in the suture line are readily apparent and can be closed quickly by the use of additional sutures. The bronchial stump is now covered

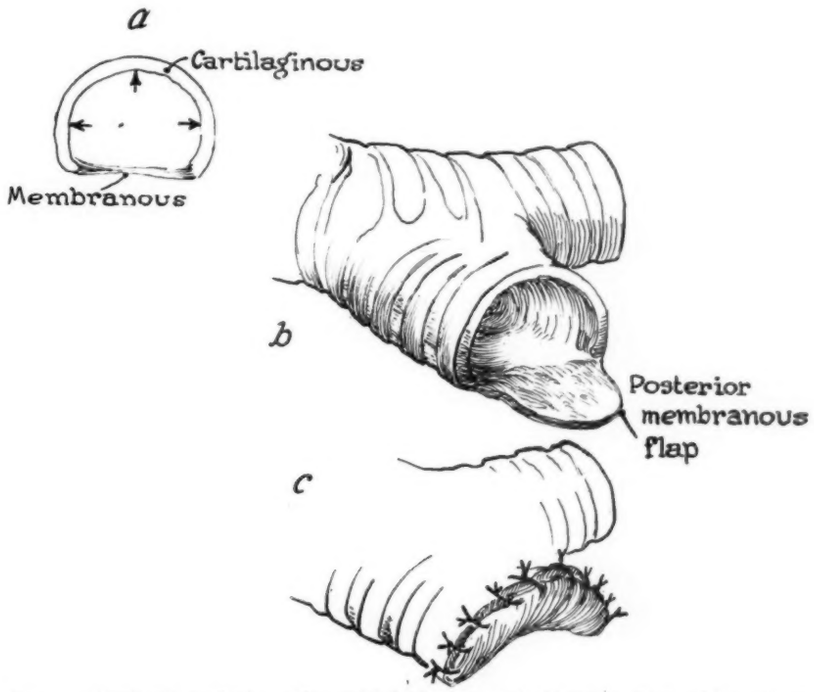

FIG. 2. Author's technic of bronchial closure. (*a*) Cross section of bronchus shows spring-like cartilage and pliable but fragile membranous portion. (*b*) Bronchus divided, membranous flap developed. (*c*) Membranous flap sutured to cartilaginous wall with interrupted sutures, 3 mm. apart and 3 mm. deep.

by the mobilized fat graft, fixed in place by at least four sutures placed equidistant around the circumference of the bronchus. (Fig. 3.)

EXPERIMENTAL OBSERVATIONS WITH THE PEDICLED PERICARDIAL FAT GRAFT

In our original series of experimental animals the pedicled pericardial fat graft reinforcement

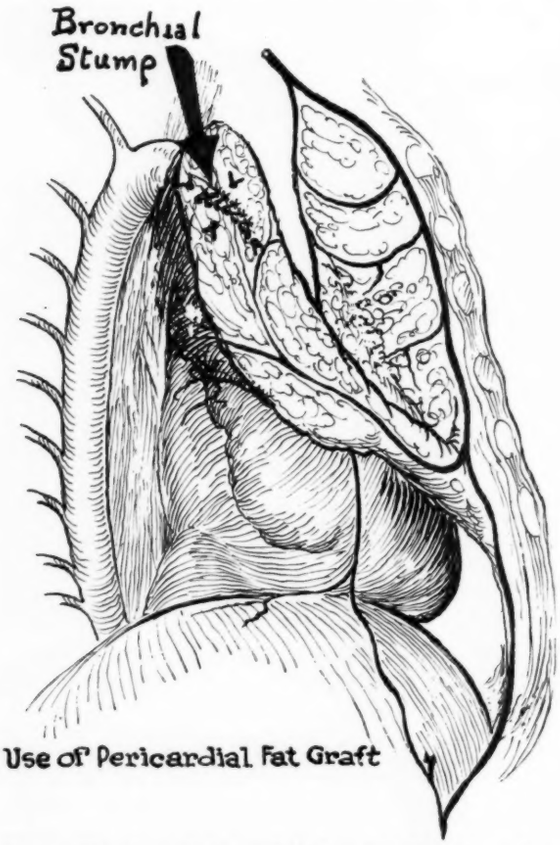

FIG. 3. Fixation of the pedicled pericardial fat graft to the bronchial stump. Four or more interrupted, fine silk sutures placed at equal intervals around the bronchus insure an airtight reinforcement.

was used to cover over the incompletely closed bronchus in twenty-one dogs.[1] In all instances the grafts were effective in sealing over these apertures and no bronchopleural fistula developed. The blood supply to the pericardial fat graft is not as extensive in the dog as in the human being, and the amount of adipose tissue is less. However, the grafts were found to be viable. By the third day on microscopic section fibroblastic proliferation formed a permanent union with the fat graft and the bronchial stump. In eight days columnar epithelium lined the defect filled by the graft. By one month's time the portion of the fatty tissue next to the bronchus showed adult fibrous tissue, with some extension peripherally. Slight increase in the fibrous tissue was found on observations up to one year. Recently we have made an additional study of a series of nine dogs operated upon with the above technic in which the viability of the fat graft was observed for periods up to two years. Results in this newer series confirmed that of the original group. Grafts were viable and intact, and effectively reinforced the incompletely closed bronchial stump in all instances. No change in the microscopic appearance of the graft was noted in the second year.

CLINICAL RESULTS IN PULMONARY RESECTION

We have employed the pedicled pericardial fat graft in 293 cases of total pneumonectomy or lobectomy. The results of this larger series are very similar to those of our original report. There have been no bronchial fistulas before the third week following operation. This means that in no case was bronchial fistula a problem during the early critical postoperative period when the reopening of the bronchus can be a disasterous complication. No patient died as a result of the bronchopleural fistula. Thus, this dreaded complication had ceased to be a clinical problem in the early weeks after surgery. However, there was an occurrence of late bronchopleural fistulas after the third week and up to the seventh month of 2.0 per cent. There is wide variance in the literature regarding the early incidence of bronchopleural fistula. The average is, perhaps, from 8 to 15 per cent. Late fistulas are generally not reported. In all instances the late occurring bronchopleural fistulas in our series closed with simple drainage of the empyema, except where there was recurrent carcinoma in the bronchial stump. Furthermore, in cases in which empyema developed the empyema was localized and the morbidity was not great.

There have been three instances when an aspirating catheter has been passed inadvertently through the right bronchial stump following pneumonectomy during the first twenty-four hours after operation. In all of these cases a portion of the trachea had been removed along with the right bronchus so that the bronchial stump was a continuation of the right lateral tracheal wall. Leakage of air was sudden and profuse. In less than one hour

marked subcutaneous emphysema was present, which in one case involved subcutaneous tissues from scalp to scrotum. The prompt insertion of a catheter in the second intercostal space, which was connected to an underwater drainage system, allowed for the escape of air coming out through the bronchial stump. In each one of these cases the thoracic omentum had been used to reinforce the bronchial stump. In each instance the leaking aperture sealed off in thirty-six hours or less and there was an uneventful recovery. Prior to the use of the pedicled pericardial fat graft we would have taken these patients to surgery to resuture a leaking bronchial stump during the early hours after operation.

Bronchial fistula occurring six months after surgery probably develops on the basis of bronchial disease and peribronchial infection. It is quite likely in the pneumonectomies that organisms close to the bronchial stump, surrounded with fibrin and clot, are thus amply protected from antibiotics placed in the pleural cavity following surgery. After a period of time a loculated pleural abscess close to the end of the divided bronchus may erode through the line of closure and a fistula develops. It is of considerable interest that we have had a number of cases of empyema following pneumonectomy in which the divided bronchus, protected by the pedicled pericardial fat graft, did not develop a bronchopleural fistula. Table 1 shows cases of pulmonary resection in this series in which the thoracic omentum was used to reinforce the bronchial stump. The operative mortality for this group was 2.5 per cent.

TECHNICS OF PLASTIC AND RESECTION PROCEDURES ON TRACHEA AND BRONCHI

Bronchotomy. Bronchotomy and closure of the bronchus represents the simplest type of bronchoplastic operation which was successfully performed by Goeltz[6] and Eloesser.[7] The bronchus may be opened at either longitudinal or transverse plane, the pathologic process removed from the wall of the bronchus and small portions of the bronchus itself excised. If a portion of the bronchial wall has been excised, closure of the bronchus in the transverse plane usually will preserve the lumen of the bronchus and only shorten its length to a negligible amount. (Fig. 4.) Of course, if a larger portion of the bronchial wall is excised, some sort of a bronchial replacement will have to be made. In performing bronchotomy care must be taken so that the sutures do not pull together the walls of the bronchus and thus produce a stricture. Furthermore, if there is too much tension on the suture line, the sutures will cut through and a fistula will certainly develop unless the graft of "thoracic omentum" has been used. In our experience the pedicled pericardial fat graft has successfully protected the bronchial closures following bronchotomy.

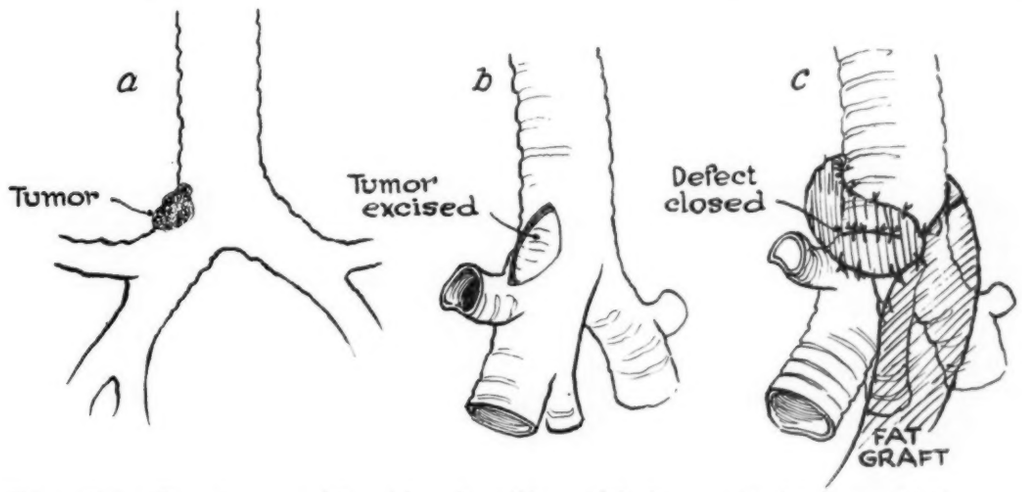

FIG. 4. Case 1. Bronchotomy with excision of small bronchial adenoma. (*a*) Adenoma of right upper lobe and main bronchus. (*b*) Bronchial wall excised in longitudinal axis. (*c*) Closure in transverse axis does not constrict lumen. Graft of "thoracic omentum" seals off tiny apertures in closure.

Flap Procedures. Flaps of bronchial wall can be fashioned to reconstruct the bronchus or trachea following the removal of a lobe or lobes of the lung. This is possible mainly in benign

bronchial conditions, as reported by Gebauer,[20] for it is rare that the surgeon would preserve a flap of bronchus close to malignant tumor. With this technic a tongue of bronchial wall is preserved and drawn up over the defect like a trap door to reconstruct the bronchus or trachea. (Fig. 5.) Thus, the airway may be maintained to the orifice of a lobe which would otherwise have to be resected. In a similar manner the tracheal airway may be maintained. We have used a single layer of interrupted sutures (either silk or tantalum wire) to make the anastomosis, which is then reinforced with the pedicled pericardial fat graft.

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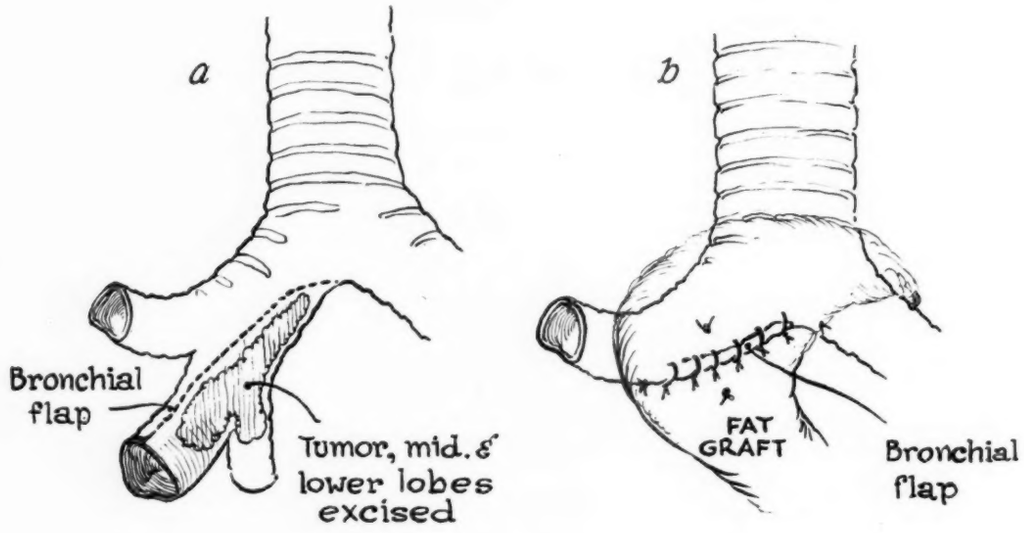

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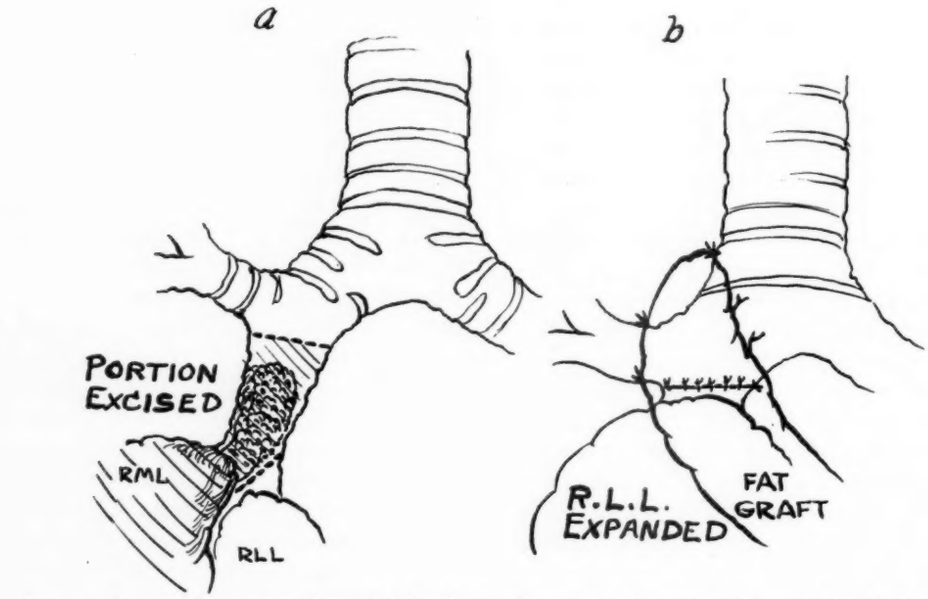


FIG. 5. Case II. Flap procedure. (*a*) Excision of tumor at bronchus intermedius including right middle and lower lobes. Lateral wall of bronchus intermedius is saved for a bronchial flap. (*b*) Bronchial flap of lateral wall of bronchus intermedius is sutured to right main bronchus and carina to preserve right upper lobe. Fat graft insures airtight closure.

FIG. 6. Case III. Lobar transplant. (*a*) Tumor of bronchus intermedius and destroyed right middle lobe are excised. Normal right lower lobe is saved with pulmonary vessels intact. Bronchus cut diagonally. (*b*) Right lower lobe bronchus sutured to right main bronchus. Diagonally cut bronchus to right lower lobe of sufficient size for anastomosis. Graft of "thoracic omentum" protects suture line.

If the closure of the anastomosis is incomplete, the "thoracic omentum" is invaluable in sealing over the apertures.

Lobar Transplants. Obstructive lesion of the main or intermediate bronchi may not necessarily mean extensive pulmonary resection or pneumonectomy. Preservation of one or more lobes of the lung may be achieved by the re-anastomosis of the peripheral but uninvolved lobe or lobes of the lung to the trachea or main bronchus after the resection of the obstructing lesion of the main bronchus, as described by Tuttle.[8] In performing this operation not only must the pulmonary artery and vein to the transplanted lobe be preserved but also the bronchial or tracheal vessels at the site where the lobar bronchus is to be re-anastomosed. Anastomosis is made with simple interrupted sutures, reinforced by the "thoracic omentum." (Fig. 6.) Constriction or torsion on a bronchial lumen is to be avoided or atelectasis of the grafted lobe will result.

Trachea or Bronchial Replacement. Considerable experimental experience has now accumulated with the resection of trachea or bronchus and replacement of the bronchial wall by artificial or fresh and preserved portions of the trachea and bronchi from one animal to another and from one location in the same animal to another location. A review of this experience is outside the limits of this communication. However, it should be recorded that small transplants are well tolerated, while extensive transplants of trachea and bronchus have eventually been absorbed and replaced with scar tissue.[9–12] The bronchial or tracheal epithelium, however, may grow in from the cut ends of the host trachea or bronchus to line the graft. The absorption of the free bronchial or tracheal graft results in a constriction with diminution of the lumen of the airway. Various artificial prostheses have been developed which maintain adequate patency of the lumen of the reconstructed trachea or bronchus.[13–15] These prostheses must be rigid enough to provide a constantly adequate airway and to permit the successful raising of secretion. Airtight connections with the trachea or bronchus and the prosthetic graft is essential. It is here that the pedicled pericardial fat graft has a most important role, for it makes possible the completion of an airtight anastomosis which otherwise might be technically impossible. Three main types of grafts and prosthetic replacements have been used: (1) metal screen covered with fascia lata,[16] (2) polyethylene or metal tubes,[17–18] and (3) dermis grafts reinforced with stainless steel wire.[19] The technics of employing these grafts are depicted in Figures 7A, B and C.

CLINICAL APPLICATION OF THE RESECTION AND PLASTIC PROCEDURES (TABLE II)

Benign Tumors of the Trachea and Bronchi

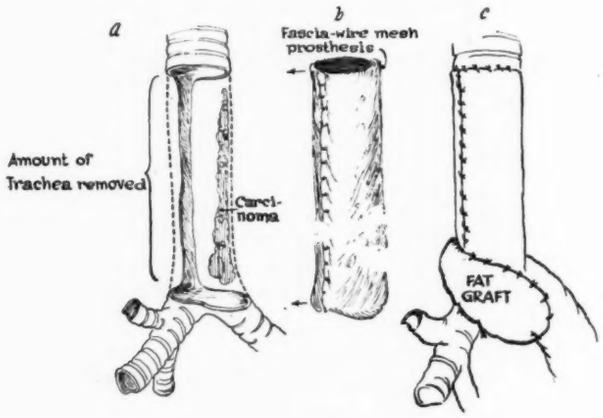
Benign tumors arising in the trachea and major bronchi may be resected with the conservation of the pulmonary tissue peripheral to the tumors, providing irreversible changes in the lung have not taken place. Benign tumors of the trachea are exceedingly rare. In 1946 Belsey[6] excised a tracheal adenoma by a right transpleural approach, repairing the defect with fascia lata reinforced with fine wire mesh. Since then a number of resections of benign tracheal tumors have been carried out.[17,21,22] We have had no case of primary benign tracheal tumor. However, in one case of a benign adenoma arising in the left main bronchus the trachea was divided in removing this neoplasm. The tracheal wall was so friable it could not be successfully repaired. With the pedicled pericardial fat graft reinforcement, an airtight closure of the bronchus and trachea was effected.

Benign tumors of the bronchi are much more common than benign neoplasms of the trachea for they make up about 5 per cent of all new growths of the bronchus. In a series of twenty benign tumors we have found three which were located in the bronchus in such a manner that they could be removed with conservation of peripheral lobes of the lung. A number of cases of resection of benign bronchial tumors have been reported with plastic procedures to conserve lung tissue.[23–25] The main technics in our cases were: (1) bronchotomy, (2) flap procedures and (3) lobar transplants.

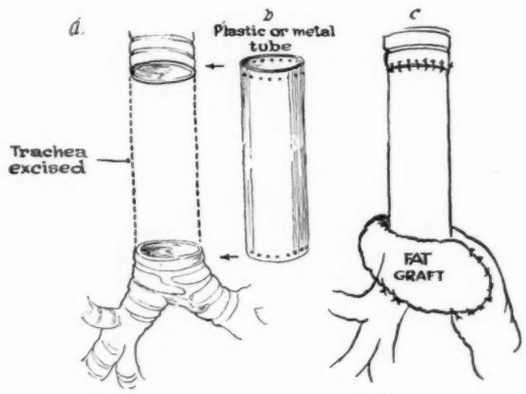
Bronchotomy for Bronchial Adenoma. A fifty year old woman (Case 1) had repeated hemoptyses over a period of eleven years. Unsuccessful attempts had been made to destroy an adenoma which was located in the right upper lobe bronchus by means of bronchoscopic fulguration. Through a right transpleural approach the trachea and right upper lobe bronchus were exposed and the tumor

excised by a longitudinal elliptic incision. Closure was effected in the transverse plane by bringing the right upper lobe to the trachea. The thoracic omentum graft made the closure airtight. (Fig. 4.) The right lung expanded completely and has remained so for over a period of two years. Pre- and postoperative x-rays are shown in Figure 8.

Flap Procedure for Bronchial Adenoma. A thirty-six year old woman (Case 11) had the signs and symptoms of a progressive pulmonary infection due to an adenoma arising in the right upper lobe orifice. X-rays revealed collapse of the right middle and lower lobes which had been destroyed by the prolonged bronchial obstruction and secondary infection. (Fig. 9.)



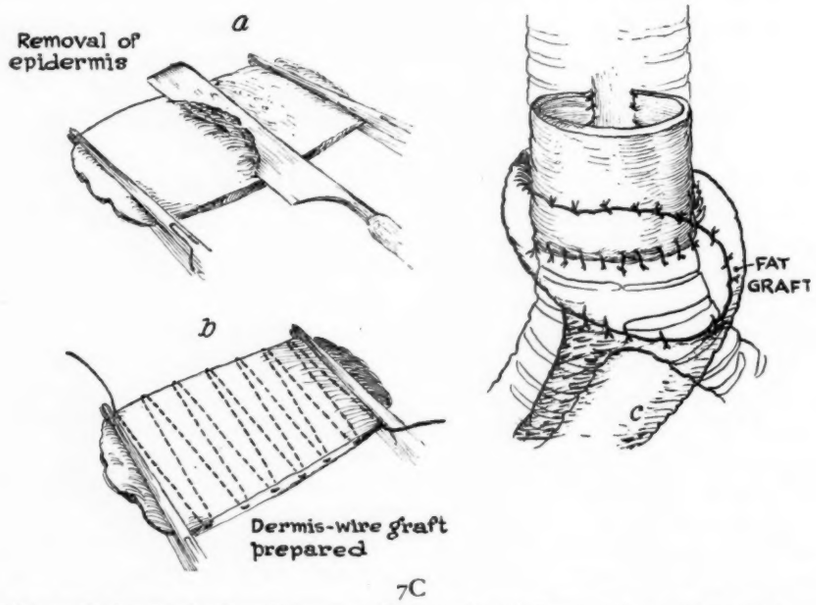
7A



7B

FIG. 7A. Case IV. Metal screen covered with fascia for extensive trachea replacement. (*a*) Extensive resection of trachea with carcinoma in right lateral wall from left thoracotomy approach. Small strand of tracheal wall on right side preserved. (*b*) Wire mesh tube fashioned around intratracheal tube. Thick strip of fascia lata sewn to mesh makes tube airtight. (*c*) Suture of fascia-wire mesh tube to right stem bronchus leaked air and was made airtight only with the reinforcement of "thoracic omentum."

FIG. 7B. Plastic and metal tubes for extensive tracheal replacement (Clagett and others). (*a*) Extensive complete excision of tracheal wall. (*b*) Plastic or metal tube with holes bored around the circumference of the wall for suturing. (*c*) Tube sewn to tracheal wall by multiple interrupted sutures. Fat graft protects inferior suture line.



7C

FIG. 7C. Dermis-wire graft for tracheal replacement (Gebauer). (*a*) Preparation of full thickness piece of skin by excising the epidermis. (*b*) No. 30 steel wire is laced through the dermis graft to provide rigidity of the wall. (*c*) Dermis-wire graft replaces excised trachea. Pericardial fat graft reinforces suture line.

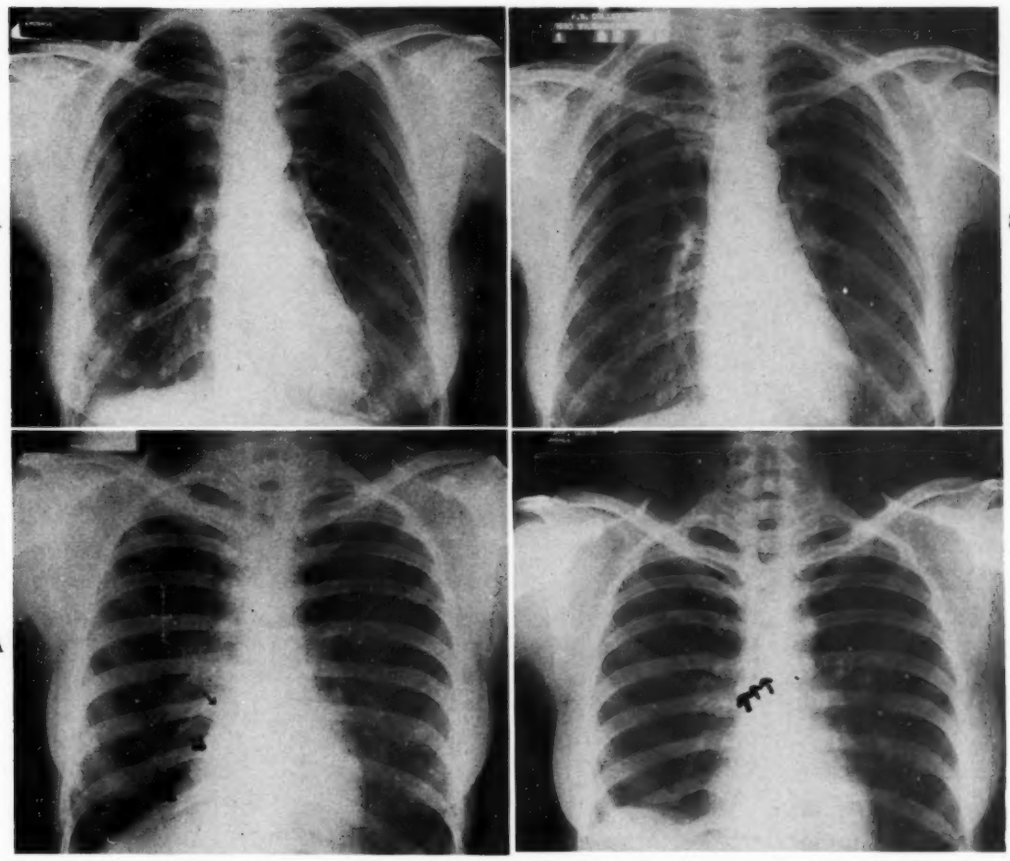
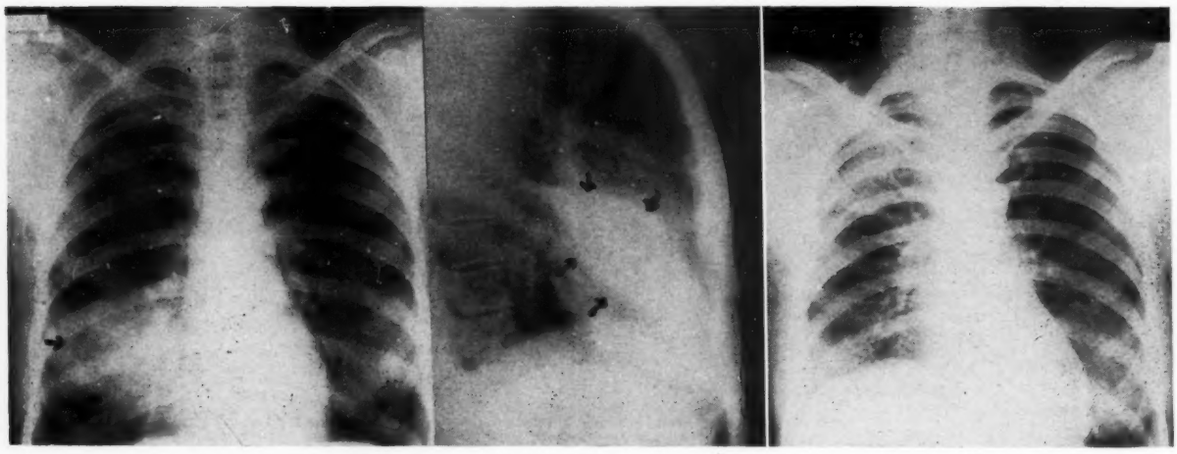


FIG. 8. Case I. A, bronchotomy with partial bronchial excision for adenoma; preoperative film shows minimal infiltration, right upper lobe. No tumor visible. B, x-ray six months after transthoracic excision of bronchial adenoma. Bronchial closure solid. Lung appears normal.

FIG. 9. Case II. A, flap procedure in resecting bronchial adenoma; preoperative x-ray demonstrates atelectatic middle and lower lobes. Upper lobe is emphysematous. Resection of bronchus intermedius and middle and lower lobes was done, preserving a flap of bronchus to preserve the right upper lobe. B, two and a half years after operation right upper lobe is completely expanded. Note tantalum sutures holding flap in place.

A right thoracotomy was performed on January 4, 1952. The right middle and lower lobes were removed. The upper lobe was saved by fashioning a flap of the uninvolved bronchus intermedius below the upper lobe and sewing this to the carina in order to preserve the airway to the right upper lobe. (Fig. 5.) This plastic closure was not airtight and the viable pedicled pericardial fat graft was needed to seal off the tiny apertures in the union. Thus the anastomosis was made leak-proof by the graft, and her recovery was uneventful. The right upper lobe expanded well and she has been without symptoms for two years, nine months. (Fig. 9.)

Lobar Transplant for Bronchial Adenoma. A forty-four year old woman (Case III) complained of recurrent pneumonia and hemoptysis due to an adenoma of the bronchus intermedius portion of the right main bronchus. X-rays demonstrated atelectasis of the right middle lobe. (Fig. 10.) However, the right upper lobe and right lower lobe were normal. On August 11, 1954, thoracotomy was performed. The right middle lobe and the bronchus intermedius were resected. The right lower lobe bronchus was then sutured to the right main bronchus at the junction of the right upper lobe. The anastomosis leaked air. However, with the help of the thoracic omentum reinforcement the suture line was made airtight. The right lower lobe aerated well. The upper lobe was slow to aerate, probably due to blood aspirated in the upper lobe, from trauma to a branch of the bronchial artery. However, in three months' time the right



10A 10B

FIG. 10. Case III. A, lobar transplant for bronchial adenoma; atelectasis of right middle lobe is shown on the PA and lateral films before operation. Two and a half months after resection of the bronchus intermedius and right middle lobe, the lower lobe which has been transplanted to the right main bronchus is well expanded. B, some residual atelectasis of upper lobe is seen.

upper lobe was almost completely aerated. (Fig. 10.)

Malignant Tumor of the Trachea and Bronchus

Primary malignant tumors of the trachea are extremely uncommon. Although a portion of the cervical trachea was removed before the turn of the century,[26] and a number have been performed since then, resection of the thoracic trachea has been reported on only a few occasions. Belsey[16] partially resected the trachea, replacing the defect with wire-reinforced fascia, leaving a small strip of the trachea in place. Clagett[17] has replaced the resected trachea by a polyethylene tube. Since then a number of other resections have been reported using the fascia reinforced with the wire mesh on a rigid plastic or metal tube or dermis graft reinforced with wire.[18,27,28]

TABLE I

SERIES OF 292 CASES OF TOTAL PNEUMONECTOMY AND LOBECTOMY EMPLOYING PEDICLED PERICARDIAL FAT GRAFT

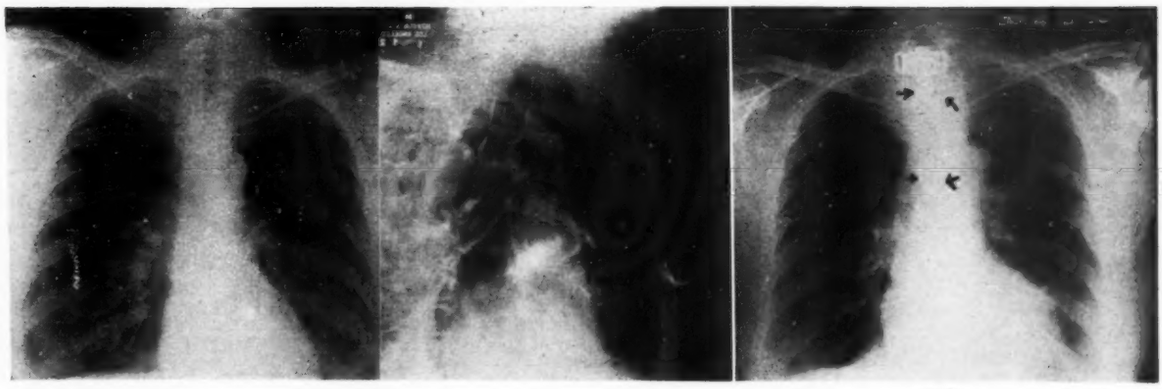
Disorder	Pneumonectomy	Lobectomy
Carcinoma (excluding cases with partial tracheal resection)	98	23
Bronchiectasis	10	61
Tuberculosis	25	42
Pulmonary abscess	...	13
Pulmonary cyst	...	4
Benign tumor	2	6
Chronic pneumonitis	...	8
Total	135	157

Extensive Resection of Trachea for Primary Adenocarcinoma. A forty-nine year old housewife (Case IV) had a cough for a number of years with exacerbation and choking spells in recent months. Although the standard chest films were not particularly abnormal, planograms and bronchograms showed a tumor at lower end of trachea. (Fig. 11A and B.) On bronchoscopy, the tumor extended on the left side from a point about 5 cm. below the larynx down to the level where the left main bronchus came off the trachea. Severe chronic bronchitis was controlled with repeated aspirations of bronchial secretion and antibiotic therapy. Because we feared it might be necessary to remove the left lung, a left-sided approach was made on March 18, 1953, through a posterolateral incision, resecting the fifth rib. Mobilizing the aortic arch, by dividing the upper intercostal vessels, the trachea and carina were

TABLE II

PLASTIC AND RESECTION PROCEDURES ON TRACHEA AND BRONCHI EMPLOYING PEDICLED PERICARDIAL FAT GRAFT

Partial excision of trachea with total pneumonectomy for carcinoma	15
Extensive resection of trachea for carcinoma	1
Bronchotomy for broncholith	2
Partial bronchial excision for benign tumor	1
Flap procedure for benign tumor	1
Lobar transplant for benign tumor	1
Total	21



11A 11B

FIG. 11A and B. Case IV. A, extensive tracheal resection for primary adenocarcinoma; preoperative standard roentgenogram shows only prominent bronchovascular markings. Bronchograms outline the tumor at the lower end of the trachea near the left stem bronchus. B, two months following extensive resection of the trachea, the lung fields are clear. The wire mesh of the reconstructed trachea is seen to extend from the level of the clavicle to the carina.

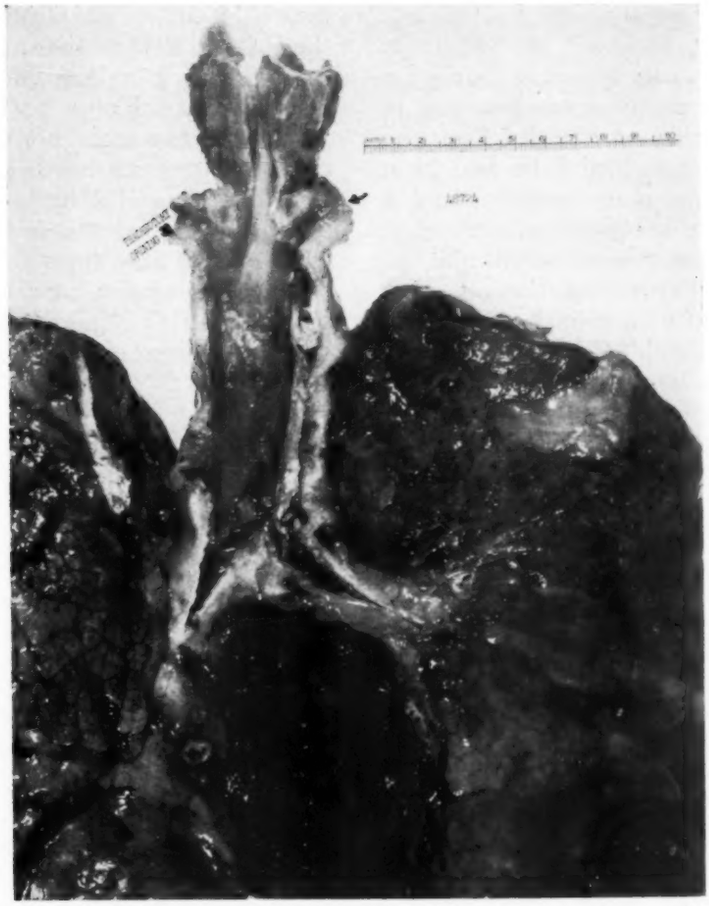
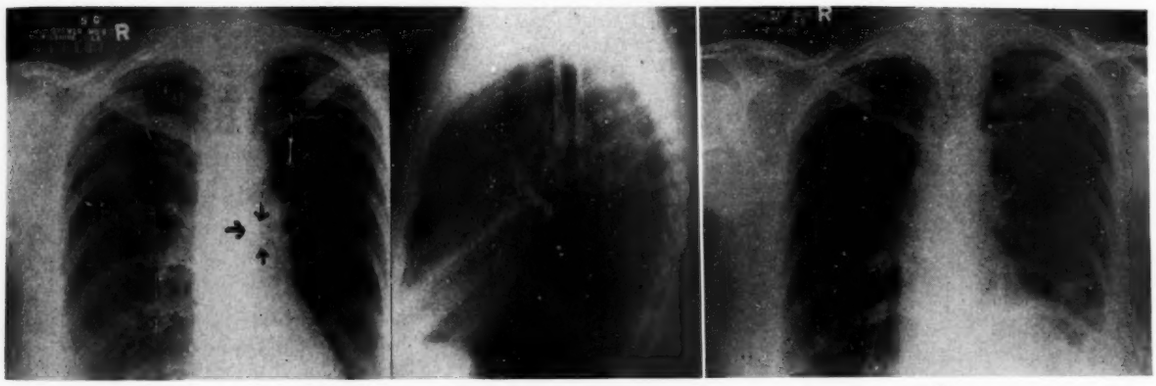


FIG. 11C. Case IV. Postmortem specimen. Death occurred 3 months after surgery from coronary occlusion. Tracheal epithelium lines completely the wire mesh-fascia tube. Cervical tracheotomy opening at upper end of prosthesis. Airway is adequate. Lung is well aerated.



12A 12B

FIG. 12. Case v. A, bronchotomy for broncholithiasis; broncholiths are shown on the posterior anterior chest film in the region of the left main bronchus. Lateral view reveals the irregular character of the stones. B, two months following transthoracic bronchotomy and excision of a "stag-horn" calculus, this stone is not seen. The left lung has some residual infiltration.

exposed. Opening the trachea the tumor extended from just above the level of the carina to the lower cervical region. Fortunately it was not necessary to resect the left lung. The tracheal tumor was resected, leaving a small strand of right posterior tracheal wall in place, from the carina to the level of the clavicle. A long intratracheal tube had been inserted into the right main bronchus and a thick fascia lata graft was placed about a steel mesh tube that had been fashioned around the intratracheal tube. Because of the difficulty of exposing the right main bronchus from the left side, it was impossible to get an airtight closure of the fascia lata-wire mesh tube and the right main bronchus. Here the pericardial fat graft wrapped around the carina saved us from a desperate situation in making the closure airtight. (Fig. 7A.) After the completion of the thoracotomy a cervical tracheotomy was performed. The tracheotomy tube entered the newly formed artificial trachea. The patient recovered from the operation, only to die three months later of a coronary occlusion. Autopsy revealed the reconstructed trachea to be a sturdy tube with a good airway. (Fig. 11C.) The tube was lined by a normal-appearing mucosa. The airway was adequate although there was evidence of recurrent carcinoma in the region of the carina. This case is of interest for a number of reasons: (1) So far as we know it is the first time the thoracic trachea has been resected from the left-sided approach with reconstruction of the trachea. (2) The pedicled pericardial fat graft made the anastomosis airtight where otherwise it would have been impossible. (3) There was complete epithelialization of the graft replacing the resected trachea, extending from the level of the clavicle to the carina.

In resecting a lung for bronchogenic carcinoma removal of a portion of the trachea along with the main bronchus is not uncommon. This technic has been reported recently by Abbott[29] and others. We have removed portions of the trachea in fifteen instances in a series of 150 resections for lung cancer. The pedicled pericardial fat graft was successful in all instances to reinforce the tracheal closure of the trachea and carina. There was one fatality in this series, not from leaking of the bronchus but from collapse of the bronchus in a case in which a portion of the tracheal wall and carina had been resected, along with the right lung. Although the remaining portions of the trachea and left main bronchus had an adequate diameter and seemed stiff enough to provide a satisfactory airway at the time of operation, the trachea and left stem bronchus collapsed following surgery. Death occurred in thirty-six hours, apparently due to respiratory failure caused by the collapse of the trachea and the left main bronchus. In this case failure to provide proper support for the trachea and bronchus could have been obviated by a securely anchored intralumenal plastic tube, or a reinforced wire graft.

Broncholiths

Broncholiths are relatively uncommon sources of bronchial obstruction, hemorrhage, or secondary infection of the lung.[30] Most

often, these stones are either coughed up or may be removed by the bronchoscope. If there has been destruction of the pulmonary tissue, secondary to bronchial obstruction, pulmonary resection is indicated. These are the usual types of reported cases found in the literature. However, if the distal lung has not been irreparably damaged, bronchotomy and removal of the stone may be indicated when bronchoscopic extraction is impossible. We have had experience with two such cases.

Bronchotomy for Broncholithiasis. A sixty year old housewife (Case v) had coughed up broncholiths for over seven years. Because of dyspnea and blood splitting medical aid was sought. X-rays demonstrated broncholiths at the left hilum. (Fig. 12.) Bronchoscopy showed granulation tissue which was thought at first to be a tumor. After removing bits of this tissue the tip of a stone was uncovered which completely blocked the left main bronchus, 1 cm. below the carina. Attempts to remove the stone through the bronchoscope were unsuccessful as this calcareous mass was firmly imbedded in the bronchial wall. On September 11, 1950, through a posterolateral thoracotomy approach, the left main bronchus was freed from surrounding structures. A long incision was made in the soft membraneous posterior wall of the bronchus, extending from a point just below the carina down to the left lower lobe. A large, two-pronged "stag-horn" type of calculus, 2 by 1.5 by .5 cm., was removed. Several smaller calculi were also lifted from the bronchial wall. Bronchotomy opening was closed with interrupted tantalum wire sutures and the suture line reinforced with a pedicled pericardial fat graft. There was no bronchial leak and the patient has been well for four years with an excellent airway in the left main bronchus, as observed on subsequent bronchoscopy.

Tuberculous Endobronchitis

Tracheal or bronchial stenosis occurs as the end result of tuberculous infection of these structures. In most instances, the tracheal or bronchial lesion is secondary to extensive pulmonary disease which, in turn, is refractory to treatment because of the bronchial obstruction. However, when the tracheal or bronchial stenosis is healed and the pulmonary disease is controlled, the stenotic lesion may lend itself to plastic operations designed to improve the airway and conserve pulmonary tissue. We have been following one case of tracheal stenosis for a possible plastic operation. However, the bilateral pulmonary disease has not yet been controlled sufficiently to permit operation. In a series of 450 cases of pulmonary resection of all types for pulmonary tuberculosis from our various services, in no instance has a bronchoplastic procedure been indicated. Experience, however, varies considerably for Gebauer,[31] in a series of 136 patients with tuberculous tracheal bronchitis, reported eleven cases in which plastic procedures to the trachea or bronchus were carried out. He has developed a dermograft reinforced with No. 30 stainless steel wire. This gives a strong graft which is stiff enough to insure patency of the airway. In ten of eleven grafts reported by him a successful result has been effected. Others have employed this technic with similar success. We believe it is the procedure of choice for small grafts of the bronchus and trachea, provided a large portion of the trachea or bronchi has not been resected.

Trauma

Injuries to the trachea or main bronchi result in the escape of large amounts of air into the mediastinum or pleura, and as such present urgent indications for emergency thoracotomy. These wounds are not common in either civilian life or warfare. One of us (L. A. B.) was privileged to treat a large number of thoracic injuries as a member of an Auxiliary Surgical Group in World War II.* In a series of 1,249 severe wounds of the chest managed by the thoracic surgeons of this group in the Mediterranean and European Theaters of Operation, there were only three instances in which bronchial laceration was an indication for thoracotomy.[32] Sanger[33] has reported the repair of lacerations of the bronchus due to penetrating missiles. Furthermore, the bronchus may also be ruptured by blunt nonpenetrating injuries, as reported by Kinsella.[34] When the diagnosis is made early, simple suture of the torn trachea or bronchus will usually suffice. If the patient survives the original wound, to go on to tracheal or bronchial stricture, a bronchoplastic operation may be indicated. However, when secondary infection results in irreparable damage to the lung

* Second Auxiliary Surgical Group.

distal to the obstruction, as in other obstructive lesions discussed previously, pulmonary resection must be employed. Pedicled pericardial fat graft is particularly indicated to reinforce the bronchial and tracheal closures in repair of wounds of these organs.

Other Lesions

We believe that plastic procedures might be employed for both congenital non-specific obstruction of the bronchus, such as those produced by the presence of a foreign body, or a localized destructive process of the trachea or bronchus. The same principles would apply to these lesions as those that have been discussed previously. It is important to stress, however, that plastic repair of trachea and bronchial obstructions must be made before irreversible changes develop in the lung tissue supplied by the trachea or bronchus.

COMMENTS

The importance of the general over-all management of the patient, including control of infection, nutrition, preoperative preparation, skillful anesthesia, postoperative care, etc., is now widely appreciated. Of course, a thorough evaluation of the pathologic lesion should be treated as essential. Thus, it must be made certain that there is no irreparable damage to the lung that is to be preserved before a plastic operation to save the lobe or lobes is decided upon. From experience gained in the management of these cases we believe that certain technical aspects should be stressed: (1) Preservation of blood supply to the bronchus and trachea and avoidance of the use of crushing clamps; (2) Use of fine interrupted sutures (.007 inches tantalum wire, No. 000 silk) with minimal trauma needles; (3) Prevention of tension on the suture line; (4) Insuring adequate bronchial or tracheal airway by non-constricting suturing and proper support of the weakened bronchial or tracheal wall by stent, wire, etc.; (5) Reinforcement of the suture line with the viable, pedicled pericardial fat graft.

After reviewing the cases presented we can conclude that when attention is paid to the aforementioned principles, the operative procedures for division and closure of the bronchus, bronchotomy, flap procedures and lobar transplants are sound and will be followed with a high degree of success. Certainly there should be no hesitation on the part of the surgeon to employ them when the occasion is presented.

While these technics are well established, replacement of large segments of the trachea represents a controversial problem. Each of the technics presented has inherent technical difficulties and the clinical experience, to date, has not been great. Because of failure to obtain airtight connections with a plastic tube in subtotal resection of the trachea in dogs, we employ the fascia lata reinforced graft in the reported case. Yet, the life of a huge fascial graft is not long and one wonders if the fibroblastic granulation tissue would always be sufficiently formed by the time that the fascia has disintegrated. We left a small strip of the posterior wall of the trachea, from the carina to the cervical region in this case. Regeneration of the mucosa was complete. Because the carcinoma recurred, a more extensive operation was desirable. There is no question, however, that this technic is excellent for benign lesions.

However, the plastic or metal tube replacement tube technic is simpler and probably permits wider resection of the trachea. If multiple point fixation can be made of the tube to the trachea, and sufficient overlap of the trachea over the tube is effected, a reasonably airtight union should be made. The fat graft will be of considerable help in protecting this connection. These plastic or metal tubes must be very firmly anchored as a permanent prosthesis to the trachea, for collapse of the fibrous-reformed trachea has been the inevitable consequence of the removal or displacement of these prosthetic tubes. If sufficient pericardial fat graft could be mobilized to cover the plastic or metal prosthesis, rapid regeneration of the fibrous tracheal wall and the mucosa could be anticipated. This would obtain for a wire mesh graft as well. The wire-supported dermis grafts have not been used for extensive tracheal reconstruction, although they have proven highly successful for partial resections of the wall. In all cases of tracheal resection of any moment it is most important that a tracheotomy tube be placed in the trachea after operation. Not only can blood and secretions be aspirated frequently through the tracheotomy tube, but also the presence of the tube prevents the development of a high positive pressure in coughing that might tear out the suture line, resulting in mediastinal emphysema or tension pneumothorax. The subsequent mediastinitis

or empyema might prove to be a fatal complication. The tracheotomy tube may be placed in the reconstructed trachea, as was done in our case.

It is certain that the last word has not been written on extensive tracheal replacement. The technics presented have proved to be effectual and further trial of these methods is warranted.

SUMMARY

1. The development and use of the viable pedicled pericardial fat graft in surgery of the trachea and bronchus are presented.

2. Our method of division and closure of the bronchus, reinforced by the "thoracic omentum" in total pneumonectomy and lobectomy has resulted in no instance of bronchopleural fistula before the third week in 292 cases. Late fistula, up until the seventh month, occurred in 2.0 per cent of all the cases.

3. The technic of resection and plastic operations on the trachea and bronchi employed by the authors is reviewed. These include: (1) bronchotomy, (2) flap procedures, (3) lobar transplants, (4) resection and replacement of the tracheal and bronchial walls.

4. A review is made of the clinical application of these technics based on personal experience in twenty-one cases. These procedures are sound and are followed with satisfactory results.

5. A wider application of these technics is possible and will result in the saving of lives and the conservation of pulmonary tissue.

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Preservation of Lung Tissue by Means of Bronchoplastic Procedures

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SEGMENTAL resection of pulmonary tissue is now a well established thoracic surgical procedure and is a particularly valuable technic in the interest of preservation of lung tissue. Bronchial anastomosis and bronchoplastic procedures in the interest of preservation of lung tissue are relatively new developments in the field of thoracic surgery. A traumatic, inflammatory or neoplastic lesion of the bronchus does not always require resection of all of the lung tissue supplied by the bronchus. By means of various types of repair it is possible to excise the bronchial lesion and preserve a portion or all of the lung tissue distal to the point of excision.

The reports of Gebauer[1–3] have demonstrated very well the merit of the concept of pulmonary salvage through bronchial reparative procedures, particularly with reference to tuberculous bronchostenosis, but including bronchial tumors. Others through individual published reports and discussion of Gebauer's papers have recorded the successful application of various reconstructive procedures of the bronchus following excision of tumors, traumatic strictures and accidental bronchial division.

TABLE 1
TRAUMATIC BRONCHIAL RUPTURE

Case	Sex and Age	Diagnosis	Surgical Procedure	Date	Result
1. L. M.	M, 22	Traumatic bronchial occlusion, right main bronchus, 7 wk. following injury	Plastic reconstruction of right main bronchus by means of dermal graft: (Plate 1, Fig. 1)	July 2, 1949	Bronchus patent; lung fully expanded
2. B. S.	M, 21	Traumatic bronchial rupture, left main bronchus, 6 wk. following injury	End-to-end anastomosis of left main bronchus: (Plate 1, Fig. 2)	August 8, 1951	Bronchus healed; lung fully expanded
3. J. C.	M, 19	Traumatic bronchial rupture, 6 hr. following injury	End-to-end anastomosis, left lower lobe bronchus to left main bronchus: (Plate 1, Fig. 3)	April 19, 1951	Bronchus healed; lung fully expanded
4. B. H.	M, 23	Traumatic bronchial rupture, 2 hr. following injury	Tracheotomy; suture of tear involving right main, intermediary and superior segmental bronchi: (Plate 1; Fig. 4)	January 20, 1954	Bronchus healed; lung fully expanded

The authors have used a variety of procedures to restore bronchial continuity and

preserve good lung tissue in eighteen patients. The bronchial lesions so treated include traumatic occlusion(2), acute traumatic rupture(2), tuberculous stenosis(3), adenoma(2) and carcinoma(9). The individual cases are summarized in Tables I to IV, with appropriate illustrations. The first sixteen cases have been reported previously.[4–6]

TRAUMA

Rupture of the bronchus may result from non-penetrating trauma of the chest. The diagnosis during the period immediately following the injury can be readily made if one keeps in mind the possibility of a tear of the bronchus in a patient who has sustained non-

TABLE II

TUBERCULOUS BRONCHOSTENOSIS

Case	Sex and Age	Diagnosis	Surgical Procedure	Date	Result
5. A. T.	F, 20	Pulmonary tuberculosis with 2 cavities persisting following thoracoplasty in 1950; healed stenosis, right main bronchus	Right upper and right middle lobectomies; plastic reconstruction of right main bronchus and lower trachea by means of dermal graft reinforced by steel wire mesh: (Plate II, Fig. 1)	December 15, 1951	Bronchus healed; good expansion of lower lobe; sputum negative
6. D. C.	F, 34	Pulmonary tuberculosis, right upper lobe; healed stenosis, right main and right upper lobe bronchi	Resection of right upper lobe and right main bronchus; end-to-end anastomosis of intermediary bronchus to trachea: (Plate II, Fig. 2)	July 30, 1953	Bronchus healed; right middle and lower lobes fully expanded; sputum negative
7. R. B.	F, 31	Pulmonary tuberculosis with destruction of right upper lobe	Right upper lobectomy which compromised the lumen of the right main bronchus; transverse division of bronchus and end-to-end anastomosis	November 7, 1953	Bronchus healed; right middle and lower lobes fully expanded; sputum negative

TABLE III

BRONCHIAL ADENOMA

Case	Sex and Age	Diagnosis	Surgical Procedure	Date	Result
8. J. S.	F, 24	Bronchial adenoma medial wall of right main bronchus	Wedge resection and transverse suture: (Plate II, Fig. 3)	June 12, 1951	Bronchus healed; lung fully expanded; well to date
9. L. H.	M, 43	Bronchial adenoma anterolateral wall, left lower lobe bronchus	Left lower lobectomy and excision of adenoma, preserving a flap of bronchial wall used for reconstruction: (Plate II, Fig. 4)	June 2, 1952	Bronchus healed; left upper lobe fully expanded; well to date

TABLE IV

BRONCHOGENIC CARCINOMA

Case	Sex and Age	Diagnosis	Surgical Procedure	Date	Result
10. L. McC.	M, 57	Bronchogenic carcinoma, epidermoid, right main bronchus, trachea and coryna, with lymph node metastases	Resection of right lung, lower trachea, coryna, and medial wall of left main bronchus; reconstruction of left main bronchus by transverse suture of left main bronchus to trachea: (Plate III, Fig. 1)	June 1, 1951	1 yr. survival; empyema and fistula developed at site of suture line which healed with drug therapy and drainage; died June 14, 1952, of carcinoma
11. V. S.	M, 56	Bronchogenic carcinoma, epidermoid, right upper lobe bronchus with lymph node metastases; emphysema with poor respiratory function	Right upper lobectomy, wedge resection of right main bronchus and transverse suture: (Plate III, Fig. 2)	November 11, 1952	Leak at suture line and empyema; healed with drainage by February, 1953; well to date
12. S. S.	M, 58	Bronchogenic carcinoma, epidermoid, left lower lobe bronchus with lymph node metastases; emphysema with poor respiratory function	Resection left lower lobe and left main bronchus; end-to-end anastomosis left upper and left main bronchus: (Plate III, Fig. 4)	April 9, 1953	Bronchus healed and left upper lobe expanded; pelvic metastasis; died August 30, 1953, with recurrence of carcinoma in bronchus and mediastinum
13. H. E.	M, 47	Bronchogenic carcinoma, undifferentiated, superior segmental bronchus, left lower lobe, with lymph node metastases	Resection of left lower lobe and portion of left main bronchus; end-to-end anastomosis, left upper lobe and left main bronchi: (Plate III, Fig. 4)	April 21, 1953	Bronchus healed; left upper lobe well expanded; well to date
14. A. B.	M, 50	Bronchogenic carcinoma, epidermoid, superior segmental bronchus, left lower lobe, with metastasis to one lymph node	Resection of left lower lobe and portion of left main bronchus; end-to-end anastomosis of left upper lobe and left main bronchi; tracheotomy: (Plate III, Fig. 4)	June 13, 1953	Emphysema relieved by tracheotomy; bronchus healed; left upper lobe well expanded; well to date
15. C. F.	M, 50	Bronchogenic carcinoma, epidermoid, right main bronchus, with metastases to regional lymph nodes; left 8-rib thoracoplasty for tuberculosis, 1946	Resection right main bronchus and right upper lobe; end-to-end anastomosis of intermediary bronchus to trachea; tracheotomy: (Plate III, Fig. 3)	June 8, 1953	Bronchus healed; right middle and lower lobes expanded well; died October 16, 1953, of carcinoma in right bronchial tree

TABLE IV (*Continued*)

Case	Sex and Age	Diagnosis	Surgical Procedure	Date	Result
16. J. K.	M, 55	Bronchogenic carcinoma, epidermoid apical posterior bronchus, left upper lobe; no node involvement	Left upper lobectomy; left lower lobe bronchus compromised by closure; wedge resection and transverse closure	March 12, 1954 March 16, 1954	Bronchus healed; left lower lobe well expanded; well to date
17. C. B.	M, 51	Bronchogenic carcinoma, epidermoid, right upper lobe; no node involvement	Resection of right upper lobe and portion of right main bronchus; end-to-end anastomosis of right main bronchus and intermediary bronchus: (Plate III, Fig. 3)	May 19, 1954	Bronchus healed; right lower lobe well expanded; well to date
18. B. C.	M, 47	Bronchogenic carcinoma, epidermoid, right, with metastases to trachea and lymph nodes	Right pneumonectomy and resection of lower trachea, coryna and portion of left main bronchus; end-to-end anastomosis of left main bronchus to trachea: (Plate III, Fig. 5)	June 28, 1954	Died July 11, 1954, of inadequate pulmonary function; anastomosis healed

penetrating trauma of the chest and in whom a tension pneumothorax and/or mediastinal emphysema rapidly develops. A bronchial tear should be suspected if following decompression of the tension pneumothorax, air continues to bubble vigorously through the water seal system and if the lung fails to expand. Bronchoscopy performed immediately following the injury will reveal in most cases the site of the bronchial tear, as it usually occurs in either main bronchus at or within a few centimeters of the coryna. However, secondary bronchi may be torn. There may be either a partial tear or complete transection of the bronchus. A great many of these injuries have ended fatally within a short time following the accident because of failure to make the diagnosis until autopsy revealed the true condition.

Prompt recognition of a traumatic bronchial rupture must be followed immediately by thoracotomy and repair of the torn bronchus, as illustrated in Cases 3 and 4. By means of an end-to-end anastomosis the left lower lobe was preserved in Case 3. The suture of a large tear involving the right main, intermediary and superior segmental bronchi resulted in the salvage of an entire lung in Case 4.

If the patient survives the early post-traumatic period, the unrepaired bronchus heals with either complete occlusion or stricture of the bronchus. Bronchial anastomosis is indicated for complete traumatic bronchial occlusion should such a patient be seen months or even years after the initial injury. Pneumonectomy is not justified unless pulmonary suppuration is present, and this cannot occur in the case of complete occlusion.[4,5] The collection of thick viscid mucus within the bronchi of the lung blocked by complete bronchial occlusion must not be mistaken for suppuration. The lung itself, although atelectatic, undergoes no pathologic change. A bronchoplastic procedure as carried out in Case 1, or an end-to-end anastomosis as done in Case 2, should be performed to relieve the bronchial occlusion and restore bronchial continuity. The atelectatic lung will re-expand and resume function if bronchial continuity is restored, even years after the initial injury. Samson and Evans[6] have recently successfully re-expanded a lung

by means of a bronchial anastomosis in a patient fifteen years after a traumatic bronchial occlusion was sustained.

The pulmonary suppuration which will develop if the bronchial tear heals by stricture formation without complete occlusion makes imperative the early diagnosis and resection of the traumatic bronchial stricture, and restoration of bronchial continuity by end-to-end anastomosis. By early diagnosis and bronchial reconstructive procedures, the mortality of bronchial rupture can be markedly reduced and lung function preserved.

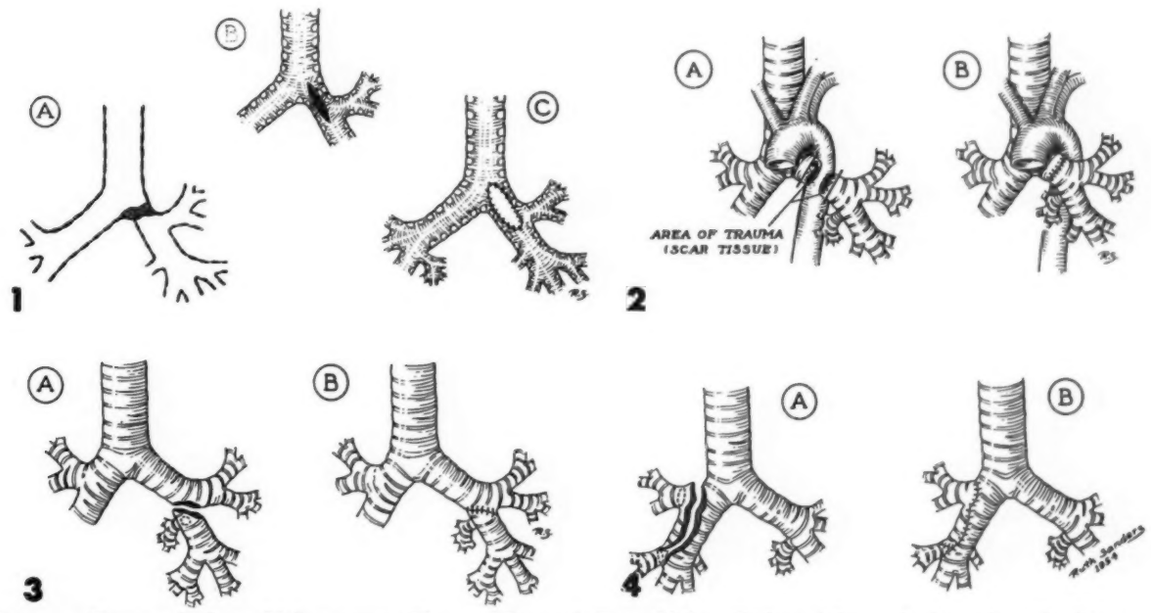

PLATE 1. Traumatic bronchial rupture. Fig. 1. (Case 1.) Bronchial occlusion right main bronchus. Incision and dermal graft seven weeks after injury. Fig. 2. (Case 2.) Complete separation of left main bronchus. Excision of scar and end-to-end anastomosis six weeks after injury. Fig. 3. (Case 3.) Complete separation of left lower lobe bronchus. End-to-end anastomosis six hours after injury. Fig. 4. Tear of right main, intermediary and superior segmental bronchi. Suture two hours following injury.

TUBERCULOUS BRONCHOSTENOSIS

Healed tuberculous bronchostenosis, usually involving the primary and secondary bronchi, may be resected and bronchial anastomoses performed. If the stenosis involves the main bronchus and the lower trachea, as in Case 5, plastic reconstruction by means of a dermal graft reinforced by steel wire mesh may be utilized after incising the stenotic area. Lobectomy or segmental resection may be performed at the same time as the bronchial anastomosis or plastic reconstruction. By re-establishing bronchial continuity the remaining healthy lobes of lung are preserved, as illustrated in Cases 5, 6 and 7. By means of these procedures a total of five lobes of lung were preserved in these patients with tuberculous bronchostenosis. There were no complications and no mortalities.

BRONCHIAL ADENOMA

Because bronchial adenoma is a tumor of low-grade malignancy, it lends itself well to localized resection and bronchial reconstructive procedures in the interest of preservation of healthy lung tissue. Only in the presence of distal pulmonary suppuration is the resection of lung tissue justified. Case 8 illustrates the preservation of an entire right lung which was healthy in spite of an adenoma in the medial wall of the right main bronchus. Wedge resection and transverse suture resulted in complete excision of the tumor with restoration of bronchial continuity.

Bronchial adenomas may be so situated that a tumor, in addition to producing suppuration in the lobe distal to it, has grown so close to another bronchial orifice as to indicate a wider bronchial resection to effect a cure. In such cases it is unnecessary to sacrifice the healthy lung tissue because a bronchoplastic procedure

or bronchial anastomosis may be carried out, which will permit wide excision of the tumor and yet preserve the healthy lobe. By means of a flap of bronchial wall it was possible to preserve the left upper lobe in Case 9. Pneumonectomy and loss of function would otherwise

instances pulmonary function may be diminished to the degree that it prohibits the resection of an entire lung but will permit the resection of a lobe. By means of a limited resection and bronchial anastomosis the removal of a carcinoma involving the right

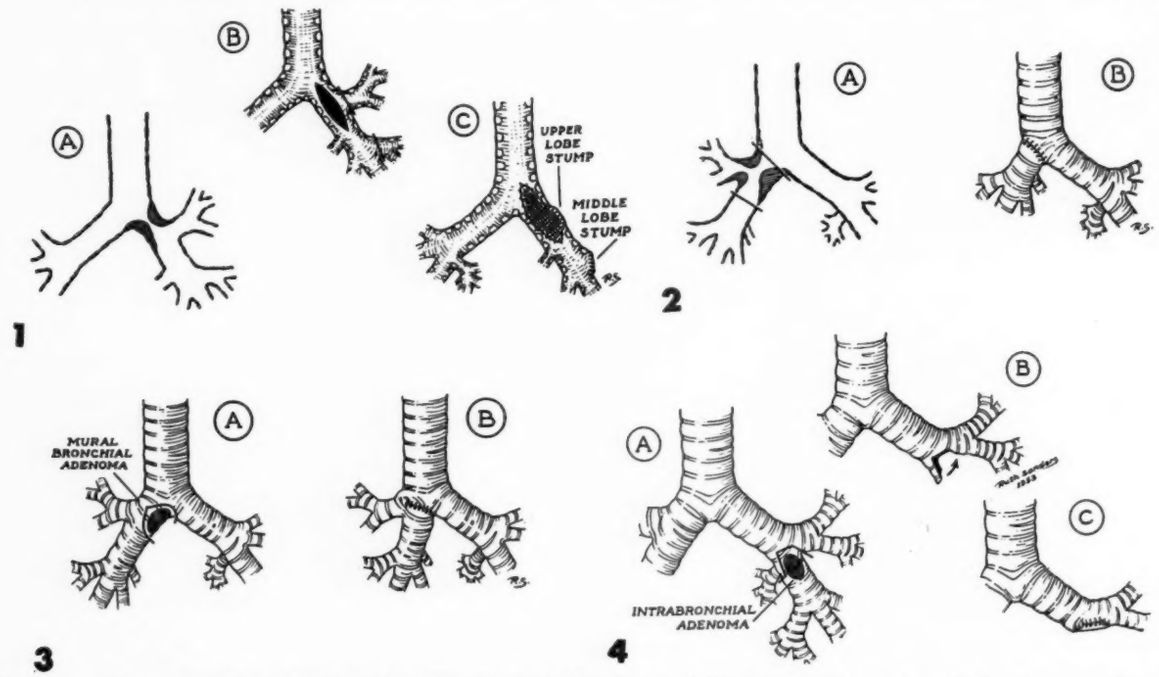

PLATE 11. Figures 1 and 2 depict tuberculous bronchostenosis and Figures 3 and 4, bronchial adenoma. Fig. 1. (Case 5.) Healed stenosis, right main bronchus. Right upper and middle lobectomies, incision of stenotic area and reconstruction with dermal graft reinforced by steel wire mesh. Fig. 2. (Cases 6 and 7.) Healed stenosis, right main and right upper lobe bronchi. Resection of right main bronchus and right upper lobe; end-to-end anastomosis. Fig. 3. (Case 8.) Mural adenoma, right main bronchus. Wedge excision and transverse suture. Fig. 4. (Case 9.) Intrabronchial adenoma, left lower lobe bronchus. Left lower lobectomy and excision of adenoma, preserving a flap of bronchial wall for reconstruction.

have been necessary for adequate removal of the adenoma.

BRONCHOGENIC CARCINOMA

The authors are of the opinion that bronchial reconstructive procedures have a definite place in the surgery of bronchogenic carcinoma under certain limited conditions. By means of transverse suture or dermal graft it is possible to restore bronchial continuity following resection of an entire lung, the coryna and a portion of the opposite main bronchus for a bronchogenic carcinoma. This procedure, as suggested by Abbott,[7] extends the operability of certain lesions which impinge upon the coryna and trachea, as illustrated in Case 10. End-to-end anastomosis of a main bronchus to the trachea is also possible following resection of an entire lung and coryna as in Case 18. In certain other main bronchus was made possible in Case 15. Pneumonectomy was out of the question because a contralateral thoracoplasty had been performed seven years before for tuberculosis. In two other cases (Cases 11 and 12) lobectomy with wedge resection and bronchial anastomosis were indicated because of poor pulmonary function. In four patients (Cases 13, 14, 16 and 18) lobectomy and bronchial anastomosis were performed deliberately on the premise that these procedures were adequate operations for these particular carcinomas.

Of the nine patients in whom a bronchial reconstruction was performed following resection for bronchogenic carcinoma, a total of ten lobes of lung were preserved. One patient died of inadequate pulmonary function twelve days following the operation. Three patients died of carcinoma, four, five and twelve months,

respectively, after the operation. It is interesting that in two of these three patients a limited resection and bronchial anastomosis were performed as a compromise with pneumonectomy because of poor pulmonary function. The remaining patients are alive and well, one, five, fourteen, sixteen and twenty-one months, respectively, following the operation. It is noteworthy that four of these five surviving patients were those in whom limited resections and bronchial anastomoses were performed deliberately as an adequate operation for their respective carcinomas.

An empyema developed in two patients, following wedge resection and transverse suture in both instances. Both responded promptly to treatment. A mediastinal and subcutaneous emphysema developed immediately postoperatively in one patient (Case 14) due to a leak of air from the bronchial anastomosis and was relieved by tracheotomy. There was one operative mortality (Case 17) twelve days after an end-to-end anastomosis of the left main bronchus and trachea following resection of the right lung and coryna. Postmortem examination revealed the anastomosis to be intact. Death was due to inadequate pulmonary function.

Recurrence of the carcinoma occurred in the reconstructed bronchial lumen in two patients (Cases 12 and 15). In each instance a localized resection and bronchial anastomosis had been performed as a compromise with pneumonectomy because of poor respiratory function.

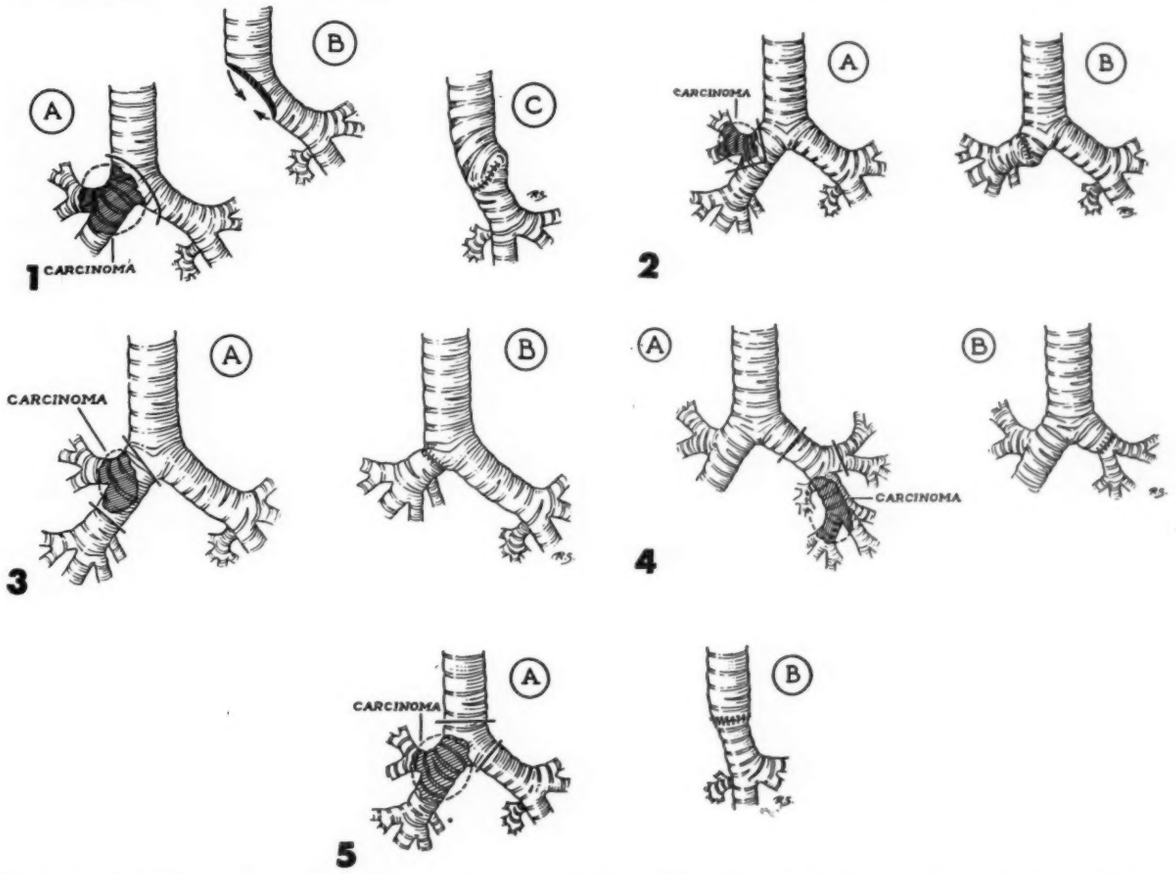

PLATE III. Bronchogenic carcinoma. Fig. 1. (Case 10.) Epidermoid carcinoma of right main bronchus, trachea and coryna. Resection of right lung, lower trachea, coryna and medial wall of left main bronchus. Reconstruction by transverse suture. Fig. 2. (Case 11.) Epidermoid carcinoma, right upper lobe bronchus. Right upper lobectomy, wedge resection of right main bronchus and transverse suture. Fig. 3. (Cases 15 and 17.) Carcinoma of right upper lobe and right main bronchi. Resection of right main bronchus and right upper lobe; end-to-end anastomosis of intermediary bronchus to trachea. Fig. 4. (Cases 12, 13 and 14.) Carcinoma of left lower lobe bronchus. Resection of left lower lobe and left main bronchus; end-to-end anastomosis of left upper lobe and left main bronchi. Fig. 5. (Case 18.) Carcinoma of right main bronchus and trachea. Resection of right lung, lower trachea, coryna and portion of left main bronchus; end-to-end anastomosis of left main bronchi to trachea.

TECHNIC

The amazing healing powers of the bronchus have been well demonstrated for years by the simple closures of bronchial stumps used by thoracic surgeons. Experimental and clinical observation with bronchial anastomoses have further substantiated this fact.

No attempts were made to preserve the bronchial vessels in this series of cases. The bronchus was cleanly divided and any bleeding from the bronchial vessels controlled. Careful suturing was done using interrupted fine cotton or cable wire sutures, so placed as to bring the mucosal edges into careful apposition. Insofar as possible the suture was placed through the bronchial wall and submucosa to avoid piercing the mucosa and tied on the outside of the bronchus. Care was taken to make the closure of the wall air-tight.

Tracheotomy was not performed routinely. The bronchial secretions, which were usually troublesome during the first few days postoperatively, were removed in most instances by means of intratracheal catheter and suction. In those cases in which pulmonary function is reduced to an extreme degree, tracheotomy should be performed at the time of the operation, as in Cases 15 and 18. Should an air leak at the site of the suture line develop in the immediate postoperative period, tracheotomy should be performed to reduce the intratracheal and intrabronchial pressure.

Postoperative bronchoscopy was avoided. Such instrumentation early in the postoperative period may traumatize the delicate mucosa at the line of suture or reconstruction. Late bronchoscopy for the purpose of inspection of the anastomotic site is unnecessary unless the patient is having symptoms, such as an irritative cough, indicating that sutures are lying within the lumen of the bronchus. Should this occur, bronchoscopic removal is indicated.

The use of the prone position during any reconstructive procedure involving the bronchus or trachea facilitates the operation considerably from the standpoint of anatomic exposure, anesthesia and maintenance of a clear airway. Because the main bronchi are situated posteriorly, the most direct exposure for most bronchial anastomoses is obtained with the patient lying in the prone position. In this position the patient tolerates an open bronchus for longer periods of time than in the lateral position because of the absence of the need for positive pressure anesthesia. Indeed, the patient may respire room air through the bronchotomy opening for short periods of time with no deleterious effects.

The airway remains clear of bloody drainage because any bleeding usually drains out into the pleural cavity rather than into the bronchus.

The passage of the intratracheal tube into the contralateral bronchus is usually unnecessary in the prone position. However, in the case of extensive resections about the coryna, this is desirable. In some instances in this series of patients the main bronchus was temporarily closed by means of a soft clamp, a sponge or interrupted fine sutures. In two instances (Cases 15 and 18) a small intratracheal tube was introduced into the distal bronchus, brought out through the wound, and the remaining lung tissue respired by means of a second anesthetic machine.

In the case of bronchogenic carcinoma the prone position makes possible an extensive mediastinal and pericardial dissection even in those instances in which a lobectomy is performed. All lymph node–bearing areas can be readily approached.

COMMENTS

There can be no question of the usefulness of bronchial suture, bronchial anastomosis and bronchoplastic procedures for traumatic bronchial rupture, tuberculous bronchostenosis and bronchial adenoma. These procedures should be considered in the surgical attack on any benign bronchial lesion to avoid unnecessary sacrifice of good lung tissue.

The utilization of these procedures in the surgical attack on bronchogenic carcinoma must be carefully considered. Inadequate pulmonary reserve and the extension of operability justify their use in certain instances. The authors are of the opinion that in the interest of preservation of lung tissue and a lower mortality, lobectomy with wide resection of the carcinoma, detailed dissection of the mediastinum, and bronchial anastomosis may be performed deliberately in those cases in which it is believed to be an adequate operation for the tumor.

Our experience with the treatment of bronchogenic carcinoma has indicated that lobectomy, where feasible, yields at least as good results as pneumonectomy, with a lower mortality. The mortality rate in our hands for the

239 resections performed for bronchogenic carcinoma during the period from 1945 to 1954 was 10.6 per cent for pneumonectomy and 3.1 per cent for lobectomy. (Table v.) The survival rates for four years or more for resections done for bronchogenic carcinoma in the

TABLE V
OPERATIVE MORTALITY FOR BRONCHOGENIC CARCINOMA 1945–1954

Type of Resection	Patients (No.)	Deaths (No.)	Mortality (%)
Pneumonectomy	141	15	10.6
Lobectomy	98	3	3.1
Total	239	18	7.5

years 1945 through 1950 are 25 per cent for lobectomy compared with 13 per cent for pneumonectomy. (Table vi.) In many instances more favorable lesions, such as the well localized peripheral carcinoma, were removed by lobectomy; although this was not entirely true, the indications being in some instances chest wall involvement and poor pulmonary or cardiac reserve.

TABLE VI
SURVIVAL RATES OF PATIENTS WITH BRONCHOGENIC CARCINOMA RESECTED 1945–1950

Type of Resection	Patients (No.)	Survivors (No.)	Survival Rate (%)
Pneumonectomy	83	11	13.2
Lobectomy	40	10	25.0
Total	123	21	17.0

Pneumonectomy is the ideal cancer operation in the majority of bronchogenic carcinomas. However, a group of localized lesions remains for which lobectomy may be a desirable and practical operation because of the lower mortality rate and the advantages resulting from the preservation of lung tissue. In addition to the indications for lobectomy already stated, this operation combined with bronchial resection and anastomosis may be considered for the well localized, small, centrally located lesions. Furthermore, this procedure will permit wider excision of the bronchus in those patients in whom limited cardiac or respiratory reserve makes lobectomy imperative.

SUMMARY

1. Bronchoplastic procedures are feasible and are indicated under certain conditions to preserve healthy lung tissue. A traumatic, inflammatory, or neoplastic lesion of the bronchus does not always require resection of all of the lung tissue supplied by the bronchus.

2. The authors have used a variety of procedures to restore bronchial continuity in eighteen patients. The bronchial lesions so treated include traumatic occlusion, acute traumatic rupture, tuberculous stenosis, adenoma and carcinoma.

3. The indications for the use of bronchoplastic procedures with resection for bronchogenic carcinoma in nine patients were inadequate pulmonary reserve in three, to extend operability in two, and deliberately for small centrally located lesions in four patients. One operative mortality occurred due to inadequate pulmonary function following resection of an entire lung, coryna and trachea. Three patients died of carcinoma within one year of the operation. The remaining five patients, in four of whom the operation was performed deliberately, are alive and well one, five, fourteen, sixteen and twenty-one months, respectively.

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Spontaneous Pneumothorax

WITH EMPHASIS ON TREATMENT

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ALTHOUGH the etiology of spontaneous pneumothorax is sometimes unknown, the most common reported cause is rupture of an emphysematous bleb. Formerly, tuberculosis was thought to be one of the more common causes; now it is known to be a rather rare cause of this condition. The onset of spontaneous pneumothorax does not necessarily occur during a period of straining or heavy lifting, but most often occurs during normal activity. In a recent review of eighty-four cases of spontaneous pneumothorax it was discovered that in all but two of the incidences, the pneumothorax occurred during normal activities.[1]

This condition is seen most frequently in young males between the ages of twenty and forty. Although Wilson has reported five asymptomatic cases, it has been our experience that symptoms are always present.[1,3] In order of frequency the symptoms are: pain in the chest, dyspnea and cough. Because symptoms are always present, no case should be unsuspected and undiagnosed. A chest x-ray will always confirm the diagnosis.

It is important that all cases of spontaneous pneumothorax be recognized and treated, because if untreated it may be fatal. When death occurs, tension pneumothorax is usually responsible. Due to a check-valve mechanism at the point of pleural leak, the intrapleural pressure builds up, causing increasing atelectasis on the affected side and progressive shift of the mediastinum to the unaffected side. Death results from inadequate oxygenation and torsion of the great vessels.

Spontaneous pneumothorax may be treated by a variety of methods, and all are acceptable in most instances. At the present time there are three principal methods of treatment for this condition: (1) bedrest alone; (2) aspiration of air from the pleural space by thoracentesis; and (3) closed thoracotomy with catheter water-seal drainage.

It is true that most pneumothoraces will re-expand with bed-rest alone. The principal disadvantage to this treatment is that it takes a month or more to re-expand the lung. During this time the patient is unable to work, remaining in bed at home or in the hospital. Because of its frequency in young males, the breadwinner of a family may be unable to work for one month or more. The second modality of treatment, aspiration of the pleural space, has a disadvantage similar to the first, namely, that it takes an average of twenty-two days to re-expand the lung. In contrast to the foregoing, when closed thoracotomy is used, complete re-expansion occurs on the average of three days.

In all cases of spontaneous pneumothorax with more than minimal collapse we advocate the third method of treatment. Yore and Morgan,[5] Hughes and his associates,[2] and others[1,3] have had excellent results with the closed thoracotomy treatment. It is time saving for both the patient and his physician. Because the lung expands rapidly (three days or less), the patient is able to leave the hospital and return to work sooner. The physician can perform a closed thoracotomy more rapidly than he can do a thoracentesis and air aspiration. In addition, it is comforting for him to know that the water-sealed drainage is a safety valve preventing tension pneumothorax.

Closed drainage prevents other complications including empyema, bronchopleural fistula and captive lung. Expansion of the lung, filling the pleural space, will prevent all three of these complications. Empyema occurs when there is a persistent air space which eventually becomes infected, or when a bronchopleural fistula re-

mains open with continuous soiling of the pleural space with tracheobronchial pathogens. In all cases of spontaneous pneumothorax a small bronchopleural fistula exists. In some instances if the lung is not expanded, the fistula will remain open. Rapid expansion causes the pleural surfaces to be opposed, thereby sealing the leak. If a pneumothorax is present over a long time, with or without a bronchopleural fistula, a non-expandable or "captive" lung may result. Its treatment, of course, is decortication, either with enzymes or by surgical means. Had the lung been rapidly expanded, this would not have occurred.

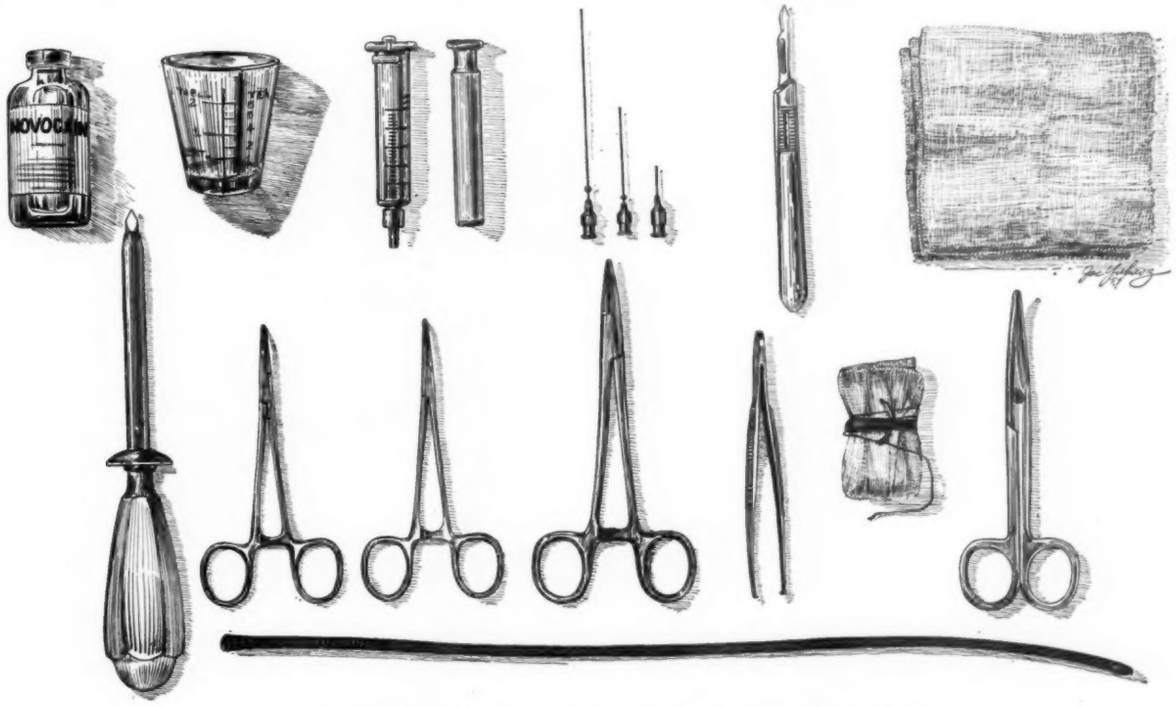

FIG. 1. Necessary equipment for insertion of the intercostal catheter.

The technic of establishing catheter drainage is simple and the necessary equipment is universally available. An ordinary paracentesis set, which is available at all hospitals, contains the equipment. (Fig. 1.) It includes a trocar, catheter, scalpel, syringe, hypodermic needles, tissue forceps, mosquito forceps, medicine glass, procaine, needle holder, needles, silk and a few sponges. The skin, subcutaneous tissue and pleura over the second or third intercostal space in mid-clavicular line are infiltrated with procaine. A small transverse incision just large enough to accommodate the trocar and cannula is made. The trocar and cannula are then plunged into the pleural space, the trocar withdrawn and the catheter passed into the pleural space through the cannula. (Fig. 2.) The cannula is then withdrawn over the catheter and the catheter sutured to the skin. The catheter is then attached to the water-sealed bottle, and a dry dressing is applied around the catheter and over the wounds.

The water-sealed bottle acts as a check-valve, allowing air to escape during coughing or expiration, but no air returns during inspiration. Negative pressure is established within the pleural space, and under most circumstances the lung expands rapidly. (Fig. 3.) In event the bronchopleural fistula is large, gentle suction may be applied to the water-sealed bottle, so that air is withdrawn from the pleural space more rapidly than it can escape into the space through the fistula.

This same general plan of treatment is very effective in traumatic pneumothorax, where it is of equal importance to obtain rapid re-expansion of the lung.

As long as the water-sealed bottle fluctuates and air escapes through it, it is functioning and is allowed to remain. When no more air escapes and the fluid does not fluctuate in the tube, the chest catheter may be removed. To accomplish this the suture which holds the catheter in place is cut and the catheter withdrawn. It is unneces-

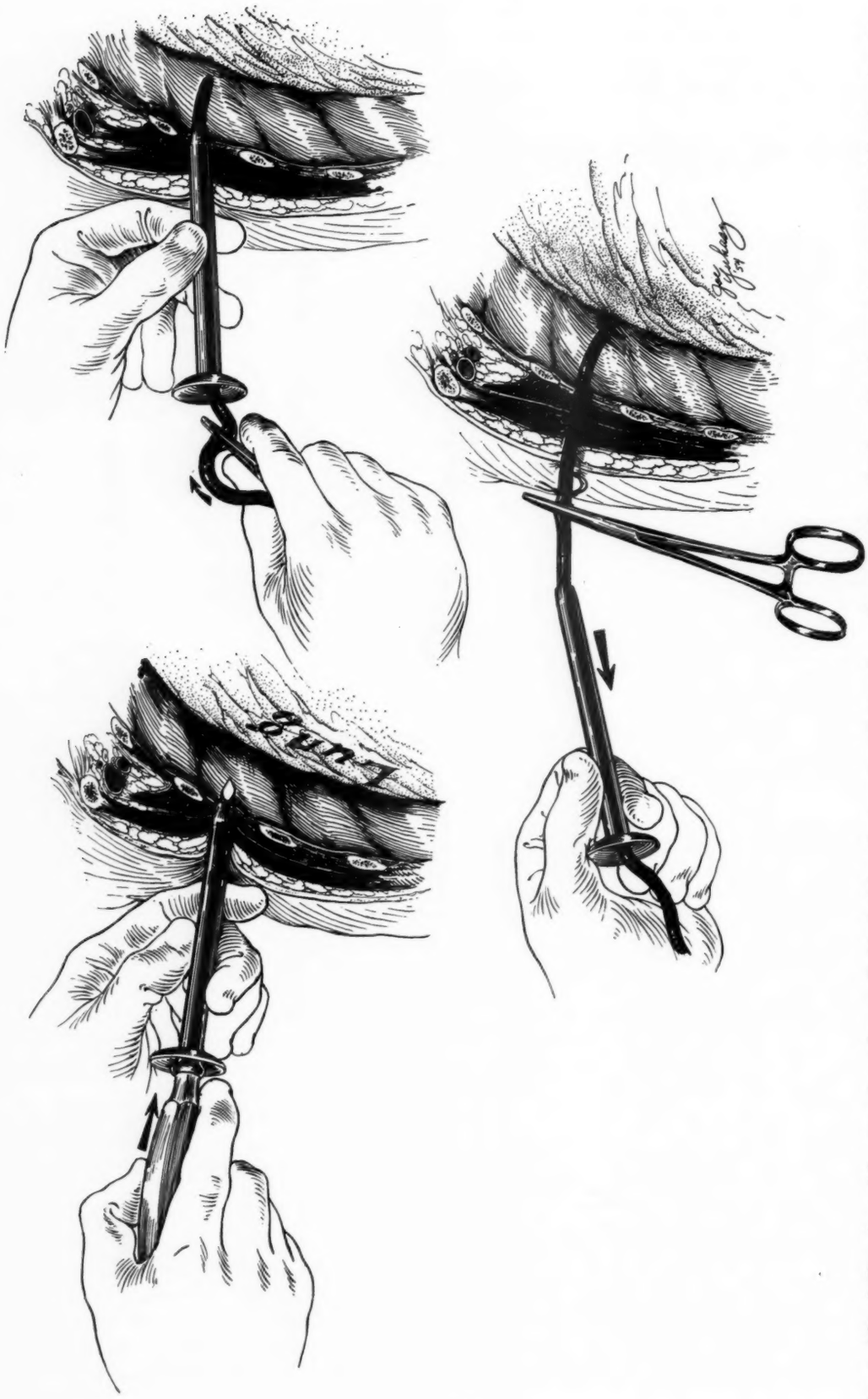

FIG. 2. After infiltration with novocain and a small skin incision the trocar and cannula are introduced to the free pleural space, bracing the guiding hand against the chest wall to prevent trocar from plunging too deeply. The catheter (usually 18 F.) is inserted through the cannula. The catheter is fixed at the chest wall and the cannula withdrawn over it.

sary to suture the catheter hole in the skin. Vaseline gauze placed over the wound will prevent air from re-entering the pleural space. X-rays and the presence of breath sounds on the affected side are of value in determining whether or not the lung is re-expanded.

pected cases. When spontaneous pneumothorax is present, it is suggested that closed thoracotomy catheter water-seal drainage be established immediately. This method of treatment is advocated because it is simple and time-saving both for the patient and for the doctor.

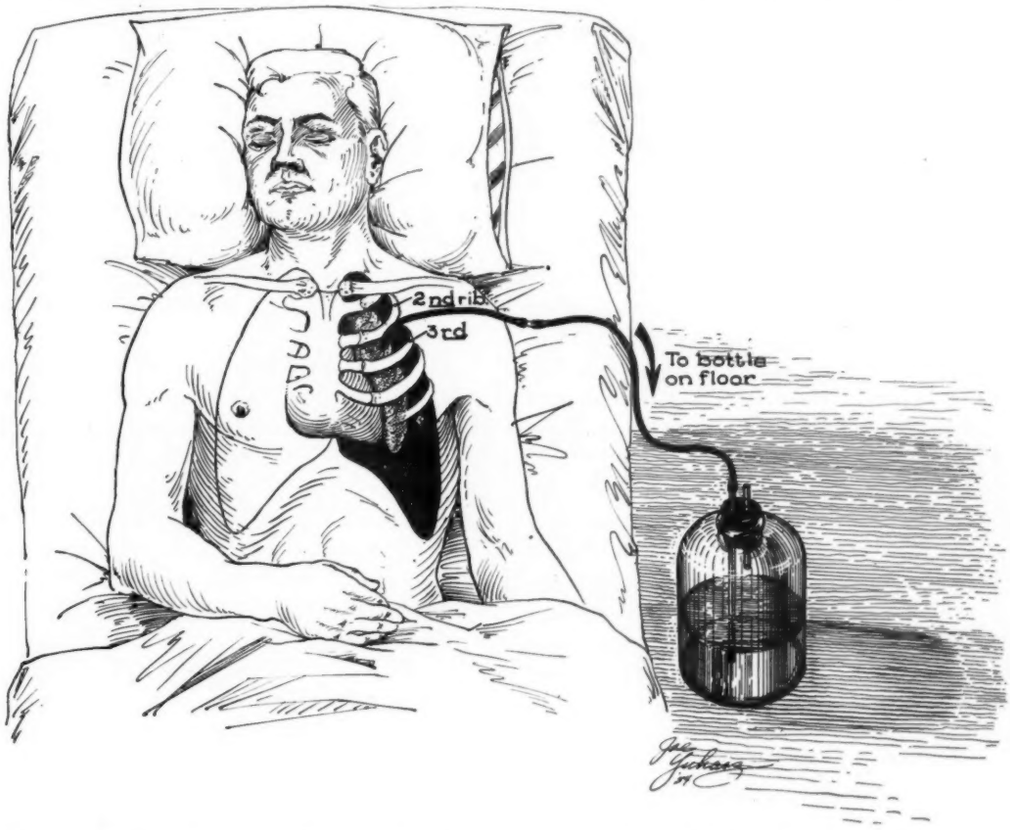

FIG. 3. Schema of water-seal system in place. The connection of the tubing to the underwater glass tube should be double-checked. Fluctuation should be visible in the glass tube.

A possible disadvantage of the closed thoracotomy is the development of empyema as a result of placing a catheter in the pleural space. This did not occur in our series.[1] The probable reason is that antibiotics were given in generous amounts, and with rapid expansion of the lung there was no potential space to become infected.

SUMMARY

Spontaneous pneumothorax is usually due to a ruptured emphysematous bleb. Ordinarily it comes on during normal activities and is not necessarily associated with pulmonary tuberculosis. It is always accompanied by symptoms, either pain in the chest or dyspnea, and so should always be diagnosed. It can be fatal and therefore diagnosis should not be missed. Chest x-ray will confirm the diagnosis in suspected cases. When spontaneous pneumothorax is present, it is suggested that closed thoracotomy catheter water-seal drainage be established immediately. This method of treatment is advocated because it is simple and time-saving both for the patient and for the doctor. If there is a tension pneumothorax, it may be life saving. Further, it tends to prevent other complications from spontaneous pneumothorax which are empyema, persistent bronchopleural fistula and captive lung.

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Spontaneous Pneumothorax

CLINICAL DIAGNOSIS AND MANAGEMENT

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HIPPOCRATES noted the succussion splash in chest disease but did not recognize pneumothorax as an entity. About 1770 Henson noted an instance of air in the thorax. Itard in 1803 first related spontaneous pneumothorax to tuberculosis. Laennec gave a full description in 1819 and suspected emphysematous blebs as a cause. This Devilliers confirmed in 1826. In 1895 Foralini first suggested its use therapeutically.[1]

The incidence of spontaneous pneumothorax varies in different reports from one in 500 to one in 1,000 in various population samples. It is two to five times as frequent in men as in women, and more common on the right side than the left.[2–5] Twenty to thirty years ago some 78 per cent were reported due to tuberculosis[5] whereas recent studies show only 6 to 10 per cent associated with tuberculosis.[6,7]

Rapport[6] suggests a classification of disease entities relating to spontaneous pneumothorax in the following simple manner: (1) structural cyst including: (*a*) congenital cystic disease, (*b*) cystic bronchiectasis; (2) inflammatory disease including: (*a*) tuberculosis, (*b*) pneumonia and pneumonitis, (*c*) abscess, (*d*) bronchiectasis and its complications; (3) emphysema including: (*a*) the obstructive types of emphysema, giant bulbous emphysema and bleb formation secondary to obstruction,* (*b*) localized distentions due to atelactasis, fibrosis, sarcoidosis, pneumonia, etc., (*c*) senile emphysema and emphysema due to chest cage deformities; (4) traumatic group including those due to violent coughing, lifting heavy weights, fractured ribs, piercing chest cage injuries, foreign bodies, etc.; and (5) idiopathic group in which no recognizable cause is found. While not all disease entities are named, this list covers in a general classified form those processes which may give rise to spontaneous pneumothorax.

The actual cause is leakage of air from the respiratory passages or alveoli into the pleural space. This as a rule is due to rupture of an alveolar septum or to a tear of the bronchial wall. Air migrates out under the pleural surface with bleb formation or ruptures into the pleural space directly. A tear in the visceral pleura may occur as a result of adhesions. Occasionally air will dissect back along the course of the bronchus instead of out toward the pleural surface. This may continue into the hilus and mediastinum and then through the visceral pleura to produce pneumothorax. Such instances are often associated with clinical evidence of mediastinal emphysema and sometimes subcutaneous emphysema. As a result of the tear, air irritation or vascular involvement there may be fluid or blood in the pleural space. In cases in which pneumothorax is due to an infectious process, there may be empyema as well.

The pneumothorax thus produced is either: (1) closed pneumothorax (following the initial leakage) which will re-expand as air is reabsorbed; (2) open pneumothorax (where there is a fistulous opening between the lung and the pleural space) which will not re-expand until the fistulous passage closes; and (3) tension pneumothorax (where a valve-like action occurs at the site of leakage) in which progressive increase of pressure pneumothorax occurs.

Acute chest pain is present in almost 100 per cent of cases. It is a sharp, cutting, tearing or stabbing pain on the affected side, seemingly pleuritic in nature. The next most common symptom is dyspnea. Next in order are sweat-

* A bleb differs from a bulla in that a bulla is freely communicative and can be collapsed whereas a bleb is due to interstitial air usually over the surface of the lungs and when pressed out in one spot moves to another without collapsing.

ing, cyanosis and, in some 10 per cent of instances, fever. Fluid may be present, either blood, pus or a serous effusion. The patient may then experience a splashing sensation in the chest. The patient usually assumes a sitting position. Pallor and sometimes cyanosis may be observed. Respiration is difficult. The affected side is usually distended with poor respiratory excursions. There may be venous dilatation over the affected side. The heart and trachea are shifted away from the affected side. Tactile fremitus is decreased. The percussion note is hyper-resonant. Breath sounds are decreased. If much fluid is present, a succussion splash can be elicited. Occasionally a whistle bubble or metallic tinkle can be heard in open pneumothorax. Coin sounds can frequently be elicited.[4,6,8]

The chief problem presented in spontaneous pneumothorax is one of disturbed intrathoracic pressure. In order to maintain respiration the chest cage and diaphragm must be able to produce enough negative pressure to expand the lungs. In open pneumothorax air exchange into the lungs is in competition with that going through the leak into the pleural cavity. Thus it is easy to see why a patient with a rigid chest cage, poor diaphragmatic movement, low vital capacity, poor lung elasticity or obstructed bronchiolar and bronchial passages does poorly with this added respiratory embarrassment. The contralateral lung is also affected by reduction of its intrapleural pressure to a significant proportion of that in the affected side.[9,10]

The dyspnea which occurs with spontaneous pneumothorax has general causes: (1) Pain increases metabolism. (2) Increased muscular effort to maintain negative pressure is necessary to maintain respiration with subsequent muscle fatigue. (3) The fact that the lungs collapse to a greater extent than usual brings into play the expiratory side of the Hering-Breuer reflex to a much greater degree than normally. (4) In the normal lung the differential circulation to various parts of the lung is due to local oxygen concentration differences. This normally prevents shunting phenomena. In diseased lungs in which these differentials are not maintained the shunting phenomena may take place with consequent reduced oxygen saturation and increased carbon dioxide retention. Both tend to produce dyspnea. (5) As the lung is changed in volume, the pulmonary vascular bed fails to act as the fluid buffer system it is normally. This may add a burden to the right heart. Further, the blood pumping action of normally fluctuating intrathoracic pressure is disturbed which further impairs circulatory function. Coupled with shunting phenomena this also decreases oxygen supply to the heart ending further to reduce cardiac efficiency. Movement of the mediastinum with respiration will impair the efficiency of the contralateral lung. The psychic response of the patient to pain and dyspnea is an additional factor which will vary from person to person.[10–14]

The following structural and functional concepts of the lungs should be a guide to therapy. First, the outer layer of alveoli are much more numerous, are of larger size, and do not have the expansive resistance of bronchi and vessels to which the inner and more medial alveoli are subject. Second, the lymphatics of the outer layer drain around the periphery to the hilus rather than along the bronchial tree. Third, the outer portion contains only small size capillary vessels. Fourth, the outer layer is the first subjected to negative pressure as it develops and thus expands first in inspiration since it has least resistance to expansion, the inner alveoli depending largely on the elongation of the bronchi to allow their expansion. Thus the outer alveoli are very important from a respiratory standpoint. Any restrictive process over these alveoli will reduce the number of effective respiratory units.[15,16] These points are of principal importance in relation to the long-term implications of therapeutic measures for preservation of pulmonary function. Further, the acute complications of spontaneous pneumothorax such as extreme respiratory embarrassment may dictate the form of therapy employed, and finally, hemothorax, pyothorax or hydrothorax further complicate the situation that must be managed.

The choices of treatment are: (1) Palliative support with bedrest, oxygen and other drugs as indicated. (2) Repeated aspirations as required: there is danger in putting a needle into the chest; for, as the lung is drawn out, new tears could be made in the visceral surface which would provide new sites for air leakage. These simple methods of management may require somewhat longer hospitaliz ation than some of the more radical methods; however, they may be justified by the long-ter m results in terms of preservation of lung function. (3)

Indwelling needle with water seal: this will undoubtedly expand the lung more rapidly. Here again the danger of the needle tearing the visceral surface of the lung is a problem. The needle in some instances is hard to keep in place. (4) Thoracotomy tube with underwater seal: this probably introduces more blood than the preceding methods and it undoubtedly causes more pleural reaction than the previously mentioned methods. These tubes, however, are easier to keep in place. The water seal has been mentioned as dangerous from the standpoint of forming a continuous fluid column from the pleural space. (5) Three-bottle suction with the Stedman pump: the bottle connected with the thorax contains only air. The second bottle contains fluid. The tube from the first bottle enters only to the neck of the second and the tube to the third bottle comes from the neck of the second to the third bottle which contains air and is attached to continuous suction. The amount of suction is controlled in the second bottle containing fluid by the depth to which a third tube communicating to room air is immersed in the fluid. As long as air is being removed from the bronchial tree to the pleural space there is no bubbling in the middle jar. When negative pressure builds up, the pump will draw air from the room through the middle bottle on inspiration. As the lung becomes expanded after the tear heals, there will be continuous bubbling in the middle bottle. (6) Thoracotomy and surgical repair of tears. This is reserved for large tears or obvious bronchopleural fistula. Decortication is usually recommended in four to six weeks following the original episode.[6,17–20]

Prevention of recurrence in patients who have had several episodes presents a thorny problem. Surgical exploration with plication of suspicious areas as well as the introduction of hypertonic glucose, talcum powder, the patient's own blood, silver nitrate, gomonol in oil, or some other irritant to cause synthesis or obliteration of the pleural space have all been tried. There are reported successes with each. The fact remains that failure is more often the rule, whatever the method employed. In general, conservative treatment is the best policy and only those patients subject to frequent recurrence should be considered for intervention of this sort. The specific measure chosen will depend on the experience of the responsible physician.[18,19,21,22]

Spontaneous pneumothorax is, then, a clinical entity which occurs with sufficient frequency that virtually every practitioner should be familiar with it. Usually an essentially benign phenomenon, at times it presents as a dire emergency. Aside from this latter situation when immediate relief of tension by needle is imperative, conservative management holds most promise for long-term preservation of pulmonary function. Treatment must be individualized. Prevention of recurrence remains the major unsolved problem.

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Some Surgical Considerations in Pulmonary Decortication

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ONE of the important advances in thoracic surgery during World War II was the rediscovery, remodeling and reapplication of "decortication."[4] In its narrowest medical sense, pulmonary decortication denotes only the stripping of a pathologic peel, cortex, fibroblastic membrane or rind from an essentially normal surface, the pleura. Since 1945 this concept has been extended to a variety of pathologic conditions and has included the development of some new surgical technics. These will be reviewed in the present paper.

The history of decortication up to World War II has been adequately covered elsewhere[22,29] and repetition would be superfluous except for emphasis on basically important points. Suffice it to say that Fowler (1893)[7] and Delorme (1894)[5] first reported the principle of the operation independently although the word "decortication" apparently was not employed until 1896 and then by Delorme.[6]

Both Fowler and Delorme recognized the process of fibroplasia within the thorax and the essential normalcy of the pleura, yet the mistaken idea of "thickened pleura" repeatedly found its way into the literature. While the correct pathologic condition was recognized by a number of individuals throughout the years, the concept of thickened pleura has also remained even to the present, both in a medical dictionary where decortication is defined as "the removal of the pleura for the relief of empyema," and in a recent French surgical volume by Iselin.[10]

With few exceptions, notably Lilienthal,[16] nearly all the original decortications were attempted on patients with chronic pleural disease. Several types of procedures were employed and results were uniformly poor by present day standards. These facts led to a virtual abandonment of the operation as a routine procedure. This has happened to other major surgical advances, discovered perhaps, too far ahead of complementary specialties for a successful outcome.

In the early days of World War II the mass effect of large numbers of soldiers with organizing and infected hemothoraces once more focused attention on the inevitable crippling and chronic invalidism resulting from these complications, attention which had rather waned between the wars. This time, however, decortication was shortly reborn. The time was ripe. Blood replacement with blood became routine; anesthetic methods had improved; thoracic surgeons were intrepid and frequently were entering the thorax in the early stages of certain diseases; antibiotics were soon to appear, although I emphasize that only the sulfas were available in 1943 when the pioneering decortications were performed.

Apparently the spark was first generated by extended discussions among thoracic surgeons of the Second Auxiliary Surgical Group early in the African campaign. The first planned decortication was for an uninfected organizing hemothorax, performed by Burford in May, 1943.[23] This operation was shortly followed by many others at the earliest overseas Thoracic Center and in September, 1943, I first demonstrated the feasibility of applying decortication to a totally collapsed lung complicated by massive post-traumatic empyema.[23] In this patient, an Italian Captain prisoner of war, there was prompt pulmonary re-expansion and primary healing in spite of the fact that the operation was performed through a completely infected field. It was inevitable that the news of successful operations such as these should travel widely, and, as so often

happens, independent observations also were made. During the latter part of the War and in the early civilian years, the American and English literature alone contained independent as well as supplementary contributions by many surgeons.[1–3,11,12,15,20,26,28,29,32]

By 1946 it was obvious that surgeons should think of applying the successful technics learned under the stress of combat to conditions and diseases more closely identified with civilian life. The extension of indications for decortication, however, has been built entirely upon its complete success in the treatment of the complications of hemothorax and is predicated on certain fundamental responses of the pleurae and pleural cavity to insult and injury. Probably these can be best understood by a brief review of the pathogenesis of hemo-organization. We still cannot explain the vagaries of the clotting mechanism as applied to free blood in the pleural cavity but the progression of organization has been followed microscopically on numerous occasions.

PATHOGENESIS OF HEMO-ORGANIZATION

Hemo-organization begins with the laying down of a thin film of fibrin and blood cells over both pleural surfaces. A closed sac or envelope is shortly formed, the "inner" surface of which is bathed by the liquid and coagulated elements of the hemothorax and the "outer" surface loosely adherent to the pleurae. Within seven days there is microscopic evidence of angioblastic and fibroblastic proliferation in this thickening layer. The process is first visible extending into the walls of the envelope from both pleural surfaces. The peel increases in thickness through the progressive organization of the clotted blood which becomes attached to the inside of the envelope. The advancing inner border of active organization remains composed of young cellular tissue and wandering fibroblasts occasionally can be seen.

Within four weeks adult fibrous tissue can be seen forming the outer portion of the peel with the fibers and nuclei arranging themselves roughly parallel to the outer surface. Most of the capillaries appear to extend into the peel at right angles to the surface, having obviously penetrated from the pleurae. The parietal segment of the peel is always thicker than the visceral, a still unexplained finding. Within eight weeks small arterioles with recognizable smooth muscle and elastic fibrils can be demonstrated in the outer or older portion of the peel. Microscopic calcium particles may be deposited in the peel within three or four weeks and this has not always been a response to infection. In some cases layers of fat cells have developed in the peel along the older or pleural surface; this may be a regressive process, a forewarning of eventual degeneration or resorption of the peel. In rare cases the peel may develop complete fibrous tissue union with the pleura which then loses its identity as a delimiting membrane. I suspect that these are cases in which there is disease of the underlying lung.

That the pleura itself does not become thickened requires continued reemphasis. For the most part, it remains a translucent elastic membrane. The occasional microscopic finding of pleural edema or a slight increase in subpleural connective tissue cannot be translated in radiologic terms. The term "thickened pleura" as used by many radiologists and others should be discarded. The complete incorrectness of this concept is obvious from the microscopic study of many decorticates of differing ages and from the knowledge of cleavage planes developed through extensive operative experience. For instance, thin, wavy elastic fibers are characteristically found immediately beneath the visceral pleura but are never seen in a resected peel unless the visceral pleura is knowingly taken with the peel and sectioned. This is well illustrated in Lindskog and Liebow[17] although I do not agree with their concept that a thickened subpleural areolar tissue will seal the alveoli. If the visceral pleura is removed, inevitably there is air leakage. In older peels, short curled elastic fibers may be found in the walls of the intrinsic arterioles. These findings are at complete variance with the description of Williams's pathologist who purported to show numerous elastic fibers in the peel itself.[32] This simply does not occur.

The development of pyogenic infection in the central fluid of the hemothorax seems to speed the process of organization and, in some instances, to make the peel tougher but there is no qualitative change which can be recognized microscopically. Continuing experience with the formation of peels associated with either a pyogenic or a specific infection confirms that the microscopic evidence of these infections is always found on the inner surface

of the peel. In the case of pyogenic infection, the fibrin and blood clot which is in the process of organization shows infiltration with polymorphonuclear leukocytes. In tuberculosis, for example, the epithelioid reaction, the giant cells, and/or evidence of caseation necrosis is only found along the youngest and most cellular (inner) surface of the peel. I have never seen diffuse infiltration of the peel by any tissue reaction which could be recognized as characteristically tuberculous.

During the war years it was common belief that there was some peculiar property of blood or blood clot which was responsible for the formation of the fibroblastic membrane. It is now known that this is a function of the pleurae, activated by a number of exciting agents in addition to blood. The peel may develop in response to pyogenic infections, specific infections (tuberculosis and coccidioidomycosis), transudates from heart failure, non-infectious inflammatory exudates (virus, chylothorax, chemical irritation), pneumothorax with or without clinical fluid, "dry pleurisy," and neoplastic effusion. Thick or thin, the fully developed membrane in each case is composed of adult fibrous tissue relatively poor both in nuclei and in blood supply. It is an inelastic membrane which keeps the lung compressed and immobilized. In all intrapleural cortices, the outer portions and the pleural "surface" of the envelope are basically the same as in organizing hemothorax, i. e., there seems to be a fundamental substrate, a common reaction of the pleura to irritation, to inflammation or to actual infection. It thus becomes obvious that decortication is only possible because all these changes are essentially within the confines of the interpleural space. Since the pleura is not ordinarily affected, a cleavage plane can be developed.

It is probable that the process of organization continues as long as fluid or air is present but ceases and remains relatively static when the envelope becomes obliterated. While the appearance of fat cells is thought to be a retrogressive process, these have been seen only in young peels and there is little evidence that adult scar tissue (the mature fibrous membrane) ever disappears from the pleural cavity.

Much of the success of decortication depends upon the condition of the lung rather than on the length of time the peel has been present. Continuing pulmonary disease means some degree of parenchymal damage and greater cellular intimacy between pleura and peel, consequently decortication may be more difficult and pulmonary expansion delayed. It is probable that this is responsible for more decortication failures than any other single factor. Prompt, complete obliteration of the pleural space is our best insurance against both the renewal of pulmonary collapse and original or recurring empyema.

INDICATIONS FOR DECORTICATION

It is difficult to give more than very general indications when considering the various types of disease in which decortication may be used.

Organizing Hemothorax and Its Complications. One must first briefly consider the newer chemical decorticants which have been more or less popular in the past few years, namely, SK-SD and tryptar.® Fibrinolysing agents have been moderately successful where the peel was composed either of fibrin or of relatively young tissue. While these agents have enjoyed a certain vogue, they have been all but discarded by a number of physicians.[30] Many patients have had severe febrile reactions following injection and good results have not been universal. Enzymatic débridement has almost always failed when used in more chronic situations in which the peel is composed of adult scar tissue.

In uninfected organizing hemothorax decortication may be considered in from three to five weeks under the following circumstances. Granted lack of enthusiasm for the injection of enzymes, decortication should be performed in a patient who has continuing thoracic discomfort, radiologic evidence of a hazy chest, a compression of 25 per cent or more of the lung with a collapsed apex, and retraction or narrowing of the interspaces. If infection supervenes in the organizing hemothorax, I recommend decortication as soon after infection is evident as the patient can be made a reasonable operative risk. Under these circumstances the operation becomes much more emergent than in an uninfected case. In infected organizing hemothorax, any degree of pulmonary compression, particularly if the apex is collapsed, would call for immediate surgical intervention.

Post-traumatic or Hemothoracic Empyema. Of course, if the patient had been followed carefully, decortication should have been

decided upon long before gross pus became evident in the pleural cavity. If, however, one is presented with such a patient, decortication should be performed as soon as the patient becomes suitable for major surgery. The indications would include a pocket of more than 300 cc., any degree of apical depression, and any presumption that there is a foreign body in the chest. In these days of multiple antibiotics, sensitivity tests should be undertaken prior to surgery so that the patient has his best chance to be protected against invasive infection. The presence of a clostridial empyema (frequent in war, rare in civilian life) would make no difference as to the treatment. The decision as to the necessity for preliminary rib resection drainage rests entirely upon the condition of the patient. If he can be made a sufficiently good risk by means of the usual supportive therapy, primary decortication should be undertaken[2] and preliminary drainage is then not only unnecessary but also unwise. Most often, patients with acute and subacute empyemas can be sufficiently improved without preliminary drainage. Occasionally in a patient with chronic empyema, wasting and debilitation, stop-gap external drainage may be necessary prior to decortication.

Finally, there is the problem of the old neglected fibrothorax with or without calcification. A symptomatic thoracogenic scoliosis may be present. Even at this late date decortication may be indicated. It is possible to remove a cuirass of calcium which will give better function to the chest wall and which may well allow subsequent corrective surgical therapy for the scoliosis.[13]

Miscellaneous Pyogenic Infections. Indications for decortication in these cases are not quite as clear-cut as in hemothorax. Primary decortication is not indicated in smaller empyemas with expanded pulmonary apex; our medical confrères have cured many of these by aspiration, lavage and the injection of the proper antibiotic. The time-honored method of adequate dependent rib resection drainage is likewise almost a certain cure for the usual posterior and lateral pocket. On the other hand, one may be faced with a massive empyema and chronic subtotal collapse of the lung or with a smaller empyema unobliterated even by adequate drainage. In such patients supportive therapy plus early decortication will give a high percentage of cures.[20,26] Decortication should shortly follow the decision (regardless of how long this is delayed) that the lung will not expand under the regimen being used.

Miscellaneous Irritative or Inflammatory Effusions. This group covers such varied diagnoses as postviral pleural fluid, effusions of unknown etiology, evanescent leakage without infection from a neighboring viscus such as stomach, esophagus or liver and chylothorax. In the past, effusions of this sort have been treated most often by repeated aspiration, with the acceptance of "pleural scar" and immobile thorax, or by drainage if a pyogenic infection supervened after multiple thoracenteses. There is no doubt that decortication is frequently indicated in this type of pleural inflammatory reaction. Continuing experience with these irritative exudates has shown that a peel may develop relatively soon, often within a week or two. If it becomes evident that pulmonary re-expansion, obliteration of the pleural cavity and restoration of good respiratory function will be impossible under conservative management, decortication becomes urgently indicated as an early procedure.

The development of a neoplastic effusion may rarely be an indication for exploratory operation with decortication and/or parietal pleurectomy. When the diagnosis is known, thoracotomy may still be undertaken because of the increasing difficulties of frequent aspirations. In such cases, it has been found that the lung is tied down by a non-specific fibrinous sheet whereas the parietal pleural element of the peel is composed primarily of shaggy neoplasm. In several such instances we have performed decortication of the visceral pleura and a subtotal parietal pleurectomy not, of course, for cure but in an effort to do away with difficult and painful thoracenteses. In two cases of pleural lymphoma with effusion this goal has been achieved.

DECORTICATION IN PULMONARY TUBERCULOSIS

Apparently Gurd's report caused a renewal of enthusiasm for decortication in tuberculosis;[8] Mulvihill,[18] Weinberg[31] and others[14,19] added important technical contributions. The invaluable protection afforded by streptomycin and other antituberculosis drugs against invasive infection and spread in tuberculosis cannot be overestimated.[24] Assuming stable surgical technics, these agents given on a

long-term basis have made decortication in tuberculosis safe. A combination of operations is frequent. Thus decorticaton may be the main procedure, it may share importance with thoracoplasty and/or resection, or it may even be a relatively minor maneuver accompanying lobectomy.

In tuberculosis the pre-existing conditions of the underlying lung and bronchi are of prime importance in a decision for or against decortication.[25] Therefore, wherever possible, serial x-rays of the chest must be reviewed including those prior to pneumothorax or pneumoperitoneum. Preoperative bronchoscopy is mandatory. Knowledge of extensive though healed tuberculosis or of bronchial stenosis (each suggesting a poor re-expansion potential) may not contraindicate an advisable decortication but it would counsel the necessity for a concomitant thoracoplasty to reduce the size of the pleural space.

Both tuberculous pleura effusion and primary empyema have been followed by static lung compression. For all practical purposes, the lung must be considered normal and, therefore, expandable. Hence decortication is indicated. An effective pneumothorax may be complicated by the development of a peel and a non-expandable lung. Fluid may persist or increase due to the development of high negative pressures when attempting to expand the lung. Empyema may develop. Decortication is frequently very useful under these circumstances often combined with resection and/or a small tailoring thoracoplasty depending on the condition of the underlying lung. The alternative procedure, with which we were all too familiar in the past, is an extensive deforming thoracoplasty. Ineffectual pneumothoraces with pleural complications are still occasionally seen and here again decortication (almost always combined with resection) appears the procedure of choice. There is a fairly large group of cases in which decortication is now being performed almost casually as an accompaniment of resection. In these, due either to a former pneumothorax, dry pleurisy, or whatnot, there has developed a thin, translucent but inelastic glove over the remaining lobes. This must be removed else the remaining lobes will expand poorly and the success of the resection will become thereby jeopardized.

Finally, there remain a few patients whose lungs were captive because of a constricting peel and who obliterated a pneumothorax space more by mediastinal and cardiac shift than by pulmonary re-expansion. Some of these patients complain of dyspnea, tachycardia and thoracic discomfort or actual pain. Poor respiratory excursions are obvious. In one patient a heart murmur developed, apparently the result of cardiac torsion. Selected individuals in this limited group can be helped greatly by thoracotomy and total removal of the scar which has immobilized the lung and the thoracic parieties.

TECHNICS OF PULMONARY DECORTICATION

Many factors, including developmental contributions, have caused variations in the performance of this operation. The age of the peel, the presence or absence of infection, the condition of the underlying lung and whether or not appreciable pulmonary or chest wall surgery was envisioned also have been important determinants. Perhaps the actual technic employed is not as important as the remembrance of the basic aim to be accomplished: complete emancipation of the lung.

The incision has become fairly standard: a posterior and lateral thoracotomy of generous length. Personally, I prefer to remove a rib because I believe that a more secure chest wall closure can be performed. There seems to be no object in making a fetish of an intercostal incision. In general, fine non-absorbable suture material is used throughout. If raw lung tissue needs to be repaired, I use fine catgut on an atraumatic needle. Electrocautery is a great time saver and is always at hand.

In what might be termed the simplest or basic type of case, that of organizing hemothorax, the interior of the envelope is entered directly by incision through the parietal pleural segment. The central contents together with all shaggy detritus are evacuated. Sharp incision is made through the visceral segment of the peel and by combined dissection, the cleavage plane between peel and pleura is identified. Frequently this can be aided by slight positive pressure through the anesthetic bag. As one carries this dissection from the visceral on to the parietal peel, an obliterated space can be entered where the two pleurae are in apposition and where dissection is very easy. Such apposition extends for varying distances from the hilum. It was the recognition of this plane and the ease with

which it is developed that prompted the technical contributions of Williams[32] and of Paulson.[21] They tend to enter this space first and re-expand the lung from the hilum outward, as it were, saving the removal of the visceral peel to the last. Once the lung is freed down to the hilum, any infoldings of the lobes are rectified as emphasized by Langston and Tuttle.[15] The fissures are opened; patches of older membrane not removed by the primary decortication are either peeled off, or subjected to discission. In the meantime the anesthetist has given intermittent and progressive positive pressure so that by the end of the operation in favorable cases, the lung practically fills the thoracic cavity. This seems to be a better way of obtaining re-expansion than attempting it all at once by unduly high endobronchial pressures. The diaphragm is freed and decorticated insofar as possible and the costophrenic sulcus is reconstituted. In these simple cases, I have usually not attempted parietal decortication as the results do not appear appreciably bettered. There is no absolute objection to the removal of the parietal peel, but it does not always seem to be necessary. It does increase the operating time and the bleeding. It is important that all pockets be opened. The parietal membrane must be smooth and should be thoroughly scraped. When established infection is present, however, our technic differs and routinely the parietal peel is removed. This is most often done following visceral decortication: (1) to give the patient the benefit of better aeration as soon as possible; (2) to insure pulmonary re-expansion even if the operation has to be abruptly terminated.

As stressed early by Weinberg[31] and others, when peel and empyema are chronic such as typified in long-standing tuberculous infection, it is attempted to remove the envelope completely without opening it or spilling the contents. It is surprising how often this can be accomplished even after twenty years. I am convinced, however, that on the chest wall side the parietal pleura is removed with the peel most of the time—a fact not generally appreciated.[27] Actually I do a parietal pleurectomy from preference because the cleavage plane is more easily developed extrapleurally than it is between pleura and peel and there is much less chance of breaking into the envelope. These operations are very time-consuming and it is advisable to have a great deal of blood on hand. The critical point of such an operation employing pleurectomy is recognition of the exact line where the two pleurae themselves come into apposition. When the line is reached, further extrapleural dissection is unnecessary. The cleavage plane should be changed from extrapleural to interpleural and the hilar structures identified and freed. One can then come back on the visceral pleural surface and, by degrees, complete a true decortication. When the technic is successful, a bag filled with pus may be totally removed from the thoracic cavity without leakage of contents. The advantages, particularly in tuberculous infections, are obvious. A natural extension of this means of treating chronic empyema is the technic of Sarot[27] in which the extrapleural separation is carried to the hilum and pneumonectomy performed. Thus a badly damaged lung and an extensive empyema can be exenterated en masse without spillage.

The technic of the "casual" decortication which may be associated with lobectomy is not difficult. The important point is to recognize that a thin, non-opaque peel is present and that such a peel is relatively inelastic. It is amazing how tough-fibered such peels are and it is highly gratifying to note the improvement of re-expansion following their removal. The proper cleavage plane is identified after meticulous incision of the peel with the lung supported by moderate positive pressure. Small blunt gauze or cotton dissectors will uncover glistening visceral pleura covered with meniscule punctate hemorrhages from the divided vessels entering the peel. If an air leak develops, the visceral pleural is being dissected with the peel.

Air leaks are inevitable in most decortications and for the most part can be ignored. If they are troublesome or if on expansion the amount of leakage seems unduly great, the area of parenchymal denudation may be either patched by spare peel or the edges approximated by continuous fine catgut. Postoperative adequate drainage is mandatory and two forty-caliber right angle tubes have been found useful. Rarely a third tube may be necessary. A simple water seal system is employed and it is only in the presence of undue air leakage that increased negative suction is applied.

The postoperative treatment differs in no way from other major thoracotomies. Rigorous

arm and shoulder exercises are instituted early as are Harken's remedial breathing exercises.[9]

CONCOMITANT OPERATIONS

As indicated throughout this report, decortication may necessarily be combined with other operations. If there are chest wall wounds, these should be excised and closed with separate instruments prior to making the main thoracotomy incision. The handling of sinus tracks previously established for the drainage of an empyema has varied. In the case of endocutaneous flaps of the Eloesser type (frequently used in mixed infection tuberculous empyemas) an elliptic incision has been made with removal of skin and the subcutaneous portion of the track down to the ribs. With further dissection between the ribs, a flap has been folded in and sutured to be removed with the empyema sac at later thoracotomy. Muscle and skin are then closed over the area; gowns, gloves and instruments discarded and the thoracotomy incision made with a new set-up. Dependent tube drainage sinuses may well be left alone and the same track used for the insertion of the postdecortication drainage tube. Necessary work on the inner portion of the chest wall for rib spicules, etc., or the removal of foreign bodies from the lungs must await the completion of decortication; tissue relationships can then be more accurately assessed and foreign bodies palpated.

The exact order of the concomitant operations most often employed in tuberculosis depends upon what is considered to be the main pathologic disorder. In cases of empyema or unexpanded lung, decortication would be the primary operation. On the other hand, resection of some type may be proceeded with first and decortication of varying degree then acts as a supplemental operation. Usually the decision for or against a tailoring thoracoplasty is delayed until it is seen whether pulmonary re-expansion is adequate following decortication and/or resection.

SUMMARY

The history of pulmonary decortication, particularly during and since World War II, has been briefly reviewed. It has been noted that within the past ten years, decortication has been employed in a variety of pathologic conditions. This has necessitated certain variations of surgical technic.

The pathogenesis of hemo-organization has been described. The formation of a mature peel in organizing hemothorax and in other pathologic states of the pleurae has been discussed. It has been emphasized that the development of a peel or fibroblastic membrane is a function of the pleurae and is in response to a number of exciting causes.

Indications for, and differing technics of decortication have been listed in the following morbid conditions: organizing hemothorax with or without infection; pyogenic empyemas of varying etiologies; specific pleural infections such as tuberculosis and coccidioidomycosis; persisting pneumothorax; either transudates or exudates arising from a variety of irritative, inflammatory or chemical sources, neoplastic effusions.

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PULMONARY EMPHYSEMA AND BRONCHIAL ASTHMA

The Application of Pressure, Including Exsufflation, in Pulmonary Emphysema

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THE respiration of patients with pulmonary emphysema is more seriously impaired by mechanical factors than in the case of any other chronic illness. An attempt will be made in this presentation to describe the physiologic events that follow the use of various types of pressure applied to the lungs and the frame of chest wall and diaphragm surrounding them. The effects of air pressure to inflate and deflate the lungs have been subjected to recent study, as well as physical forces applied by the patient himself, such as manual compression of the lower chest, pursed-lip breathing and breathing exercises which increase the relaxation pressure of the lungs.

Since the disturbance in the functions of the lung was originally traced to progressive distention and rupture of the alveoli, this entity was called hypertrophic or vesicular emphysema; the term "diffuse obstructive emphysema" was used to emphasize the importance of bronchial constriction as a major cause of the clinical symptomatology.[1]

Although the force exerted by the playing of wind instruments or by glass blowing has been discarded as an etiologic factor in the disease, undue inspiratory distention and expiratory check-valve mechanisms may result in the development of areas of increased pressure, especially in the apices where the soft tissues offer little counterprotection. Other explanations include atrophic or degenerative changes in the parenchyma of the lung, perhaps associated with local ischemia of the tissues.

The etiology of pulmonary emphysema is, however, obscure, the disease in most instances being of gradual onset accompanied by the symptoms of chronic bronchitis. In approximately one-third of our male patients a previous history of viral disease, especially atypical pneumonitis, is obtained within a period of two to six months before the onset of dyspnea. Studies on the pathology of pulmonary emphysema pertinent to this discussion reveal the following: (1) The respiratory bronchiole is frequently lengthened as a stem-like tube, presumably therefore susceptible to collapse by the distended alveoli surrounding it. (2) Inflammatory and fibrous tissue changes in the bronchioles produce thickening and narrowing of the lumen. (3) Impairment of the bronchial blood supply due to endarteritis of the smaller vessels impair nutrition of the lung parenchyma.[2]

In this discussion of the pathophysiology of the disease emphasis will be accorded to those disturbances in respiratory function that especially lend themselves to the application of pressure, which we have included in the term "physiologic therapy," i.e., therapeutic attempts to restore respiratory function toward the normal, primarily by the use of physical procedures. It has been customary to assume that the earliest example of this approach was the administration of oxygen, which was followed by the introduction of other gases and the varieties of pressure breathing now in use. In a recent study of artificial respiration,[3] however, mouth-to-mouth insufflation was first used by Tossach in 1743 and reported by him later.[4] Biblical records provide an even earlier example of successful application of pressure as a therapeutic agent; Elisha

revived the son of a Shunamite woman who had been apparently dead for some time by putting his lips over those of the child's and breathing into his lungs (mouth insufflation). Although this form of intermittent pressure breathing is a safe and effective method of resuscitation of infants,[3] the use of intermittent pressure breathing for the treatment of pulmonary emphysema is controversial. The employment of pressure breathing, however, whether continuous or intermittent, has a sound physiologic basis for its employment in such clinical disturbances of respiration as pulmonary edema and obstructive dyspnea. Before discussing the varieties of pressures that may be used by the technician as well as by the patient, a consideration of some of the features of pulmonary emphysema will be presented.

PATHOPHYSIOLOGY

Among the most conspicuous manifestations of impairment of respiratory function is a plainly discernible interference with diffusion of oxygen and carbon dioxide. The oxygen saturation of the arterial blood is frequently decreased between 75 and 93 per cent either at rest or after exercise. The CO_2 tension of the arterial blood becomes elevated as the disease progresses. The factors responsible for this have been listed as follows: (1) increase in residual air, namely, the volume of air present in the lungs after a deep expiration which impairs diffusion by enlarging the air column through which it takes place; (2) narrowing of the smaller bronchi as a result of inflammatory change, mucus or bronchospasm; (3) irregular aeration of the alveoli; (4) diminution of the functional respiratory surface due to the merging of small alveoli into larger air sacs; (5) progressive alveolar distention associated with check-valve mechanisms, in turn associated with bronchial constriction and impaired lung tension; (6) bronchial closure during rapid breathing and coughing, the degree varying with the relative increase in intrathoracic above the intrabronchial pressure; (7) impairment of the mechanics of breathing, including the problems encountered by the patient in effective ventilation due to a depressed, flattened diaphragm and the inefficient use of the accessory muscles of breathing. Among these influences the unequal alveolar ventilation seems to be of primary importance, since a large part of the tital volume appears to be wasted on bullous, poorly diffusing areas of the lungs.[5]

The factor of expiratory obstruction, noted more than a century ago by Laennec,[6] was then considered to be due to the presence of mucus in the bronchial tubes. The relief of bronchospasm after administration of bronchodilator compounds and inhalation of 80 per cent helium with 20 per cent oxygen, confirmed by spirometric tracings, made it clear that expiratory obstruction of the smaller bronchi was a major factor in producing dyspnea in these cases.

Recently, the ventilatory disturbance has been investigated by methods which simultaneously determined (1) the intrathoracic pressure, derived either by determining the alveolar pressure through a sudden interruption of the respiratory stream with a rapidly acting valve or by measuring the intrapleural and esophageal pressures, and (2) the respiratory air flow rate obtained by pneumotachygraphic records. Through the use of these technics the wide swings of intrapleural pressure from negative to positive during ordinary respiration were shown to represent the increased pressure required to move air in and out of the lungs in patients with pulmonary emphysema. The decreased recoiling force of the lung parenchyma (PL) was found to be only in small part the cause of the high pulmonary pressures required for ventilation, since the pressures required to move air in the bronchioles were tremendously increased, particularly during the expiratory cycle.[8,9]

The increased intrathoracic pressure developed to overcome resistance to flow of air was found to be mainly due to turbulent viscosity rather than tissue viscosity or the frictional movement of the lung itself; this conclusion was based in part on the finding that more pressure was required to move a gas of increased density, i.e., argon-oxygen mixtures.[9] The studies on retarded air flow in patients with pulmonary emphysema have revealed that bronchial closure is in part the result of impaired recoil of the pulmonary parenchyma which results in a lessened outward traction on the bronchial wall but also to the increased resistance to air flow (PV) during expiration. When the pressure gradient between the alveoli and the cartilage-supported ends of the bronchi drops lower than the

intrapulmonary pressure, cessation of air flow through smaller bronchi occurs. PT (Thoracic Pressure) = PL (Lung Pressure, negative in relation to atmosphere) plus PV (Pressure required to maintain gas flow, or drop in pressure from alveoli to pharynx.)[9]

The concept of Christie[5] that the diseased portions of the lungs fill earlier than the more normal areas was traced to their decreased "elastic" pressure. The dyspnea of the patient may be perhaps in large part due to the circumstance that a considerable proportion of the tidal volume enters bullous areas of the lung that are poorly supplied diffusing membranes and blood vessels. It was also observed at operations that the diseased areas empty less well after inspiratory inflation, because of the lessened elasticity or decreased elastic recoil.[2] The use of an intermittent pressure-breathing device does not in fact result in increase in maximal minute ventilation, vital capacity or sustained clinical benefit, if simultaneous inhalation of bronchodilator aerosols is not provided.[10,11] What happens to bullous areas of the lung inflated by I.P.P.B. during expiration is a point of interest in this connection. Crenshaw[2] has observed at operations that after application of a constant inspiratory pressure the diseased regions in the lung resist deflationary pressure whereas the more normal parts can be readily emptied.

The development of pressure breathing as a clinical method for the treatment of pulmonary edema and obstructive dyspnea consisted at first of the use of a continuous mask pressure of approximately 6 cm H_2O. The effects of this degree of pressure were briefly summarized as follows: (1) an increase in the diameter of the smaller bronchi during expiration in patients with bronchial asthma as determined by x-ray lipiodol films; (2) an increase in peripheral venous pressure of 40 per cent of the applied intramask pressure in normal subjects, 60 to 70 per cent in patients with decreased pulmonary elasticity such as those with cardiac failure; (3) marked prolongation of the circulation time in patients with cardiac insufficiency; (4) disappearance of pulmonary edema and relief of obstructive dyspnea; (5) a warning to discontinue pressure breathing if the systolic pressure fell 15 mm. Hg below its control value.[12] It was later found that expiratory pressure breathing provided by exhaling in a mask equipped with variably constricted orifices was effective in treatment of edema of the lungs although much less so in alleviating obstructive dyspnea. Nevertheless, it was observed that pursed-lip breathing, which often takes place spontaneously in patients with pulmonary emphysema, was in effect a form of expiratory pressure breathing which also increased peripheral venous pressure and enlarged bronchial diameter with immediate decrease or disappearance of wheezing rales in the chest.[12]

The development of pressure breathing as a method of increasing alveolar oxygen pressure during inhalation of 100 per cent oxygen took place at high altitudes as a technic for decreasing hypoxia. It was noted then that mean pressures as high as 15 mm. Hg, whether obtained by continuous or intermittent pressure breathing, reduced cardiac output.[13,14] Lower mean pressures such as 5 to 7 mm. Hg possessed a variable effect, at times being accompanied by reduction of cardiac output but in some cases of cardiac failure being followed by an increase in cardiac output,[15–17] perhaps due to a restoration of tone of the cardiac muscle, similar to the effect previously shown as the result of pressure breathing[12] or tourniquets applied to the legs in cases of pulmonary edema.

Although it was reported some years ago that inspiratory lung-inflating pressures followed by expiratory negative pressures had favorable effects on the circulation in dogs,[18] additional evidence was obtained that patients treated in the tank respirator adversely effected in respect to their circulatory status by pressure breathing (induced by intratank negative pressures of 15 cm. H_2O) were favorably influenced by a combination of positive lung-inflating and negative lung-deflating pressures.[19]

Exsufflation and exsufflation with negative pressure introduced as mechanical methods of eliminating retained bronchial secretions provided an opportunity to study positive and negative pressure breathing in the following respects: (1) The duration of application of inspiratory pressure was found to be a significant factor not only in increasing mean ventilatory pressure but in augmenting lung and tidal volume.[11,20,21] Thus, with a positive inspiratory pressure of 40 mm. Hg, a tidal volume of 2,500 cc. with a 1.6 second inspiration was increased to 3,800 cc. with a

3.0 second duration of inspiration. Since the hazard of tearing of an emphysematous bleb is more directly related to increase in lung volume than to pressure itself, it became evident that the duration of pressure should not be sufficiently prolonged as to result in undue

20 and 40 mm. Hg to minus 40 mm. Hg in 0.02 seconds resulted in not only a high expiratory flow rate at the start of expiration but also in a mean venous pressure actually lower than that used with a 15 mm. Hg inspiratory pressure, either in the tank respirator or in

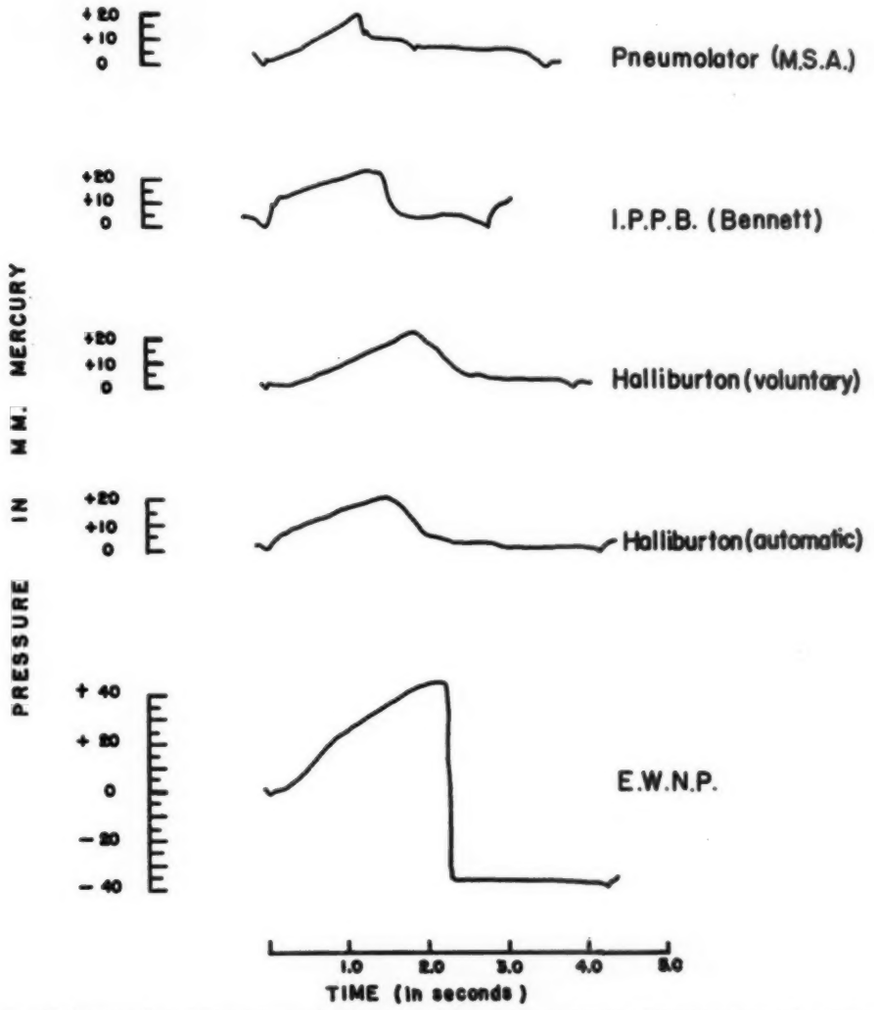

FIG. 1. The shape of the mask pressure curve is illustrated for various types of supra-atmospheric intermittent pressure-breathing devices and for exsufflation with negative pressure. In the use of E.W.N.P. the duration of expiratory pressure is 0.02 seconds as compared to 1 second or more with the I.P.P.B. apparatus. The mean pressure over a complete respiratory cycle in the subject tested was 2.5 for the Pneumolator, 7.2 with the Bennett, 5.1 for the Halliburton used with spontaneous respiration, 6.7 when used as an automatic resuscitation and −6.9 mm. Hg with E.W.N.P. The low negative mean pressure with E.W.N.P. is due to a 2 second exposure to −40 mm. Hg. When the expiratory cycle is reduced in duration, the mean ventilatory pressure becomes atmospheric or even slightly above. The graph illustrates that a mean ventilatory pressure produced by a peak 20 mm. Hg pressure may be higher than that obtained with a peak 40 mm. Hg pressure due to the abrupt cessation of pressure during expiration and the duration of the negative pressure selected.

pulmonary distention. It was also clear that a tidal volume of 2,500 cc. of the lungs might be achieved with a 20 mm. Hg inspiratory pressure maintained for 2.5 seconds. (2) The abrupt termination of inspiratory pressure between

intermittent pressure breathing devices. The graphic record on a Statham Strain guage of the character of mask pressure curves of the various I.P.P.B. apparatus employed with E.W.N.P., shown in Figure 1, reveals that the

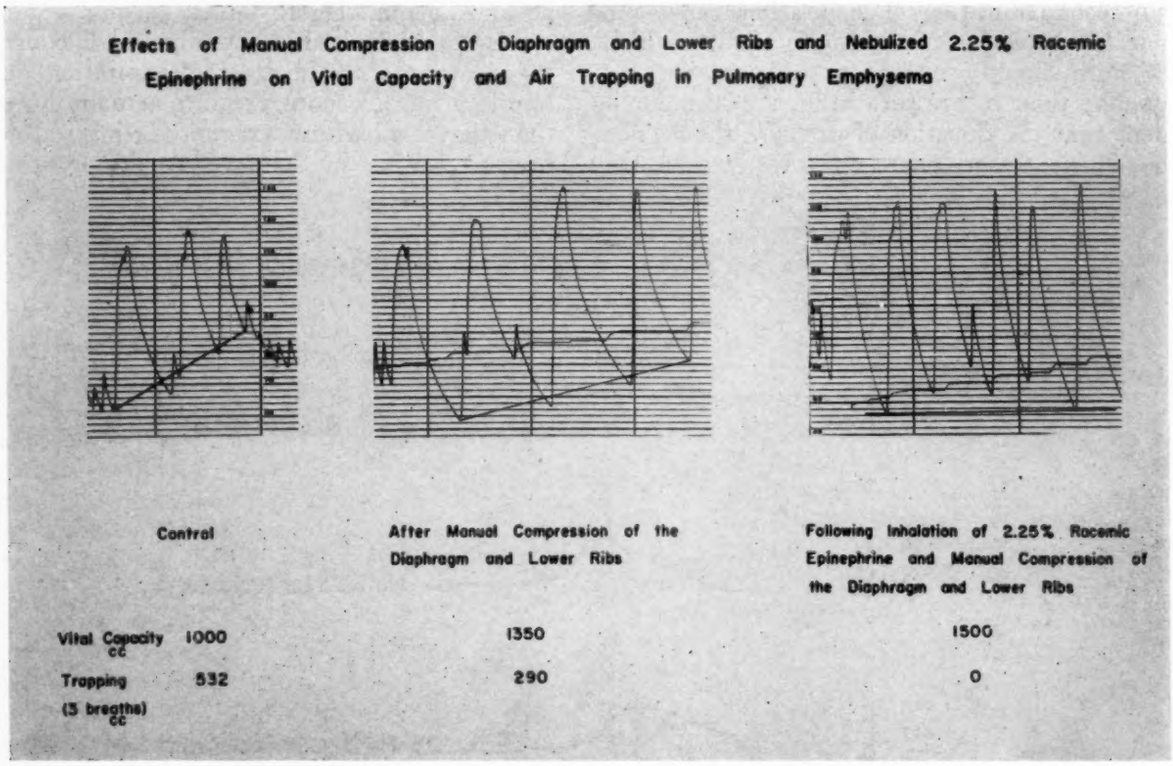
Effects of Manual Compression of Diaphragm and Lower Ribs and Nebulized 2.25% Racemic Epinephrine on Vital Capacity and Air Trapping in Pulmonary Emphysema
Control
After Manual Compression of the Diaphragm and Lower Ribs
Following Inhalation of 2.25% Racemic Epinephrine and Manual Compression of the Diaphragm and Lower Ribs
Vital Capacity cc 1000 1350 1500
Trapping (3 breaths) cc 532 290 0

FIG. 2. Manual compression of the thorax and upper abdomen resulted in diminished dyspnea, a decrease in the trapping of air after three breaths from 532 to 290 cc. and an elevation in vital capacity from 1,000 to 1,350 cc. A still further improvement was manifested when this procedure was done after inhalation of a bronchodilator aerosol (0.5 cc. vaponephrin). Trapping of air was then absent and the vital capacity rose to 1,500 cc.

expiratory phase consumes at least 1 second or more in I.P.P.B. apparatus in contrast to a duration of expiration of 0.02 seconds with E.W.N.P. The mean pressure with E.W.N.P. is seen to be negative (minus 6.9 mm. Hg) in contrast to elevated positive mean pressures between 2.5 and 7.2 and with I.P.P.B. 7.2 mm. Hg. Depending on the duration of the negative cycle the mean pressure may be made at or above atmospheric. Since the highest expiratory air velocity begins at the termination of inspiration, when the diameter of the bronchi is maximally enlarged, a swift delivery of alveolar air from the bullous areas may take place before bronchial constriction takes place. The reported increases in vital capacity that have followed the use of E.W.N.P.[21] may then be traced not only to elimination of obstructing mucous plugs but perhaps also to elimination of air previously trapped in the lungs, as has been demonstrated by the use of negative pressure breathing in the absence of administration of bronchodilator aerosols[11] and by manual compression of the lower ribs and upper abdomen, as seen in Figure 2. This maneuver, exercised with the palms placed on the lateral anterior margins of the lower three ribs and adjoining abdominal surface, is executed by a rapid series of three inward and upward thrusts of the hands, repeated on ten consecutive or alternate expirations. The result of lessened alveolar distention is manifested by a variable increase in vital capacity between 200 and 1,000 cc. In the instance seen in Figure 2, an increase from 1,000 to 1,350 cc. in vital capacity occurred without administration of epinephrine and, when performed after inhalation of epinephrine, the vital capacity rose to 1,500 cc. with complete absence of trapping of air. This maneuver was previously shown to produce increased expiratory flow rates, either when executed by itself or in conjunction with exsufflation.[11,20] Following the combined use of bronchodilator aerosols and chest compression, the pulmonary ventilation is consistently decreased, with a decrease in the difference between the pulmonary ventilation breathing air and breathing 100 per cent oxygen.[21] Although the existence of pressure during the expiratory phase of I.P.P.B. would

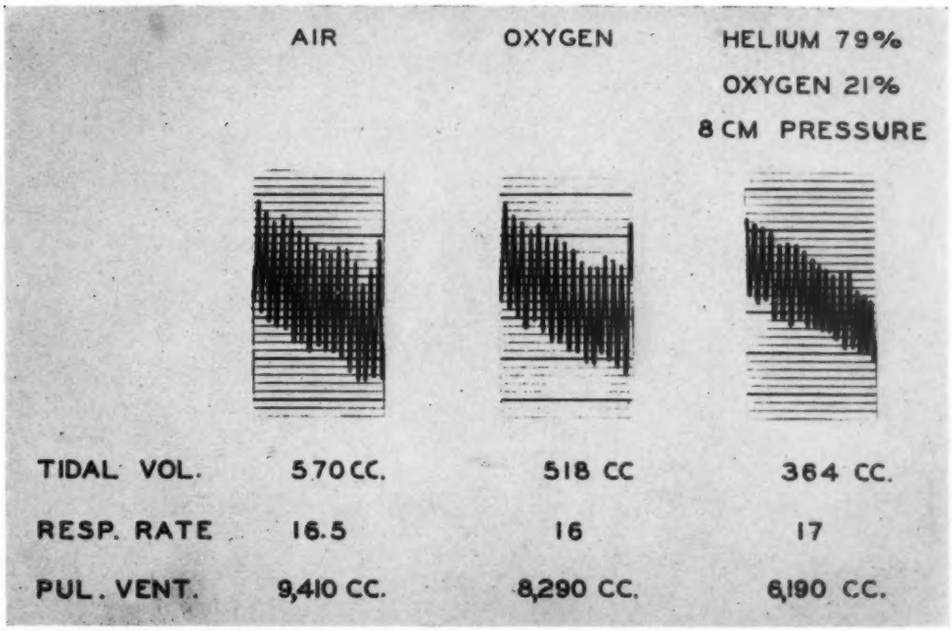

FIG. 3. Decrease in pulmonary ventilation in a patient with pulmonary emphysema when breathing 100 per cent oxygen and when breathing 79 per cent helium–21 per cent oxygen with 8 cm. H_2O pressure.

have the advantages of maintaining a wider diameter in the smaller bronchi as well as a variable effect in preventing undue pulmonary congestion, elimination of trapped air in the lungs has not been demonstrated by its use without simultaneous administration of bronchodilator aerosols.[10,11]

Another example of the effect of purely physical factors in the relief of dyspnea in patients with pulmonary emphysema is shown in Figure 3, in which a more marked reduction in ventilation takes place as a result of inhaling a helium-oxygen mixture under 8.0 cm. H_2O pressure, from 9,410 to 6,190 cc., than was found during the inhalation of 100 per cent oxygen. Under these circumstances effective ventilation of the alveoli was presumably increased by widening of the bronchi and increased gas velocity of turbulent gas flow in regions of bronchial constriction.

A similar relief of dyspnea is portrayed in Figure 4 in which a remarkable demonstration of prolonged expiration is recorded in a patient with pulmonary emphysema and fibrosis, and chronic bronchitis. Expiration consumed 86 per cent of the expiratory cycle, a manifestation of the patient's own response to the need for adequate time to empty lungs through an evidently constricted bronchial airway. Even though the helium-oxygen mixture employed contained the same concentration as that present in air, its administration with a continuous pressure of 4 cm. resulted in a decrease in pulmonary ventilation from 8,560 to 6,940 cc. per minute with a decrease in tidal air from 955 to 534 cc. The readiness with which bronchi in a patient of this type are susceptible to collapse has been commented upon in reference to the pneumotachygraphic studies of air flow. Pressure breathing, whether continuous or intermittent, would be of symptomatic benefit by increasing bronchiolar pressure and increasing lung volume, thereby preventing bronchial closure.

Exsufflation with negative pressure makes use of a high lung-inflating pressure to distend the bronchi sufficiently to pass air beyond occluding plugs of mucus. As shown by the experimental studies of Bickerman[22] on the removal of mucin-thorotrast mixtures and foreign bodies, the diameter of the smaller bronchi of anesthetized dogs was enlarged twofold, a critical factor in aerating the alveoli distal to the foreign substance. Another favorable effect of a high pressure drop such as from a mask pressure of plus 40 to minus 40 mm. Hg was considered to be the instantaneous expansion of gas, approximately one-

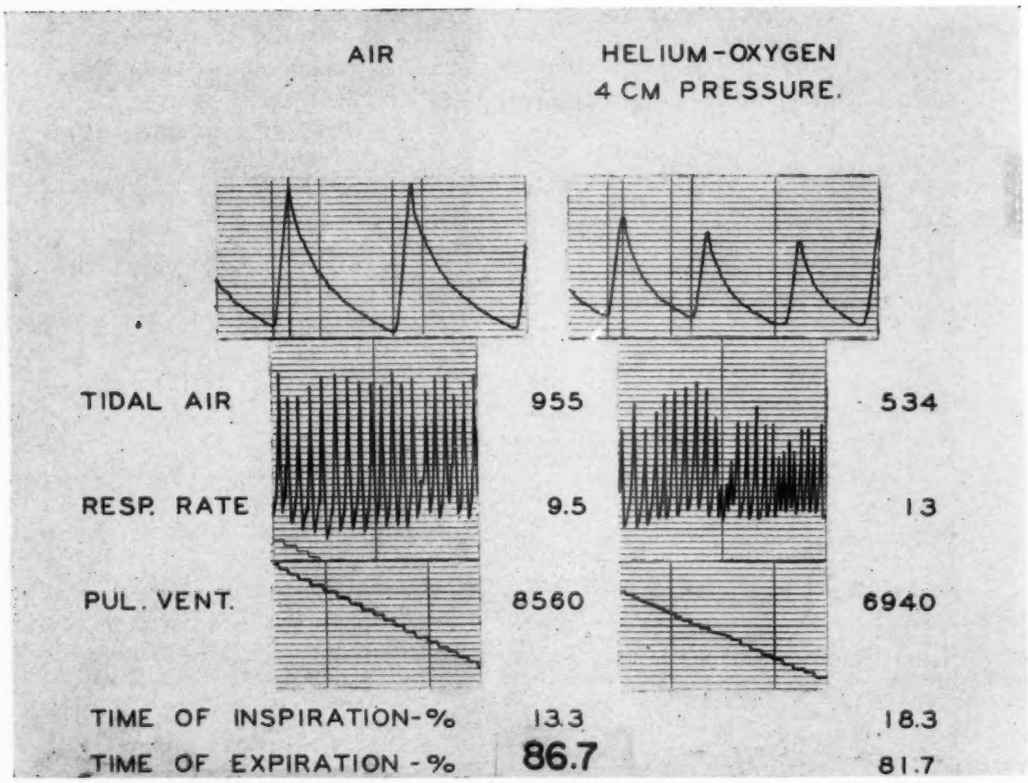

FIG. 4. Spirometric records in a patient with pulmonary emphysema, pulmonary fibrosis and chronic bronchitis reveal the unusually long duration of expiration spontaneously adopted by the patient. The diminution of dyspnea was produced by purely physical effects, namely, the inhalation of 80 per cent helium with 20 per cent oxygen under continuous pressure of 4 cm. H_2O. The pulmonary ventilation dropped from 8,560 to 6,940 cc. per minute and the tidal air from 955 to 534 cc.

tenth of an atmosphere, which contributed the factor of explosive decompression originally used in the mechanical cough chamber. The esophageal pressure being about half the mask pressure, a smaller pressure drop takes place between the bronchi and the mouth.

No harmful effect has been observed in more than 4,000 treatments in over 400 patients treated. In respect to the effect of this degree of positive pressure on the circulation it was pointed out that since the expiratory cycle was terminated in 0.02 seconds, the mean pressure of the respiratory cycle was not greater than that routinely used in I.P.P.B. and in the conventional tank respirator for patients with poliomyelitis. In regard to the more important question of inflating the lung unduly it was previously suggested that the significant factor was the duration of application of pressure; thus when the time employed in inspiration was 1.6 seconds, a tidal volume of 2,500 cc. was produced with a 40 mm. Hg inspiratory peak pressure; but a doubling of the inspiration time produced 50 per cent increase in tidal volume. If we were to disregard the factor of maximum explosive decompression, an inspiratory pressure of 20 mm. Hg is adequate to accomplish the main purpose of a full inflation of the lung and a corresponding increase in bronchial diameter. The physiologic fact of the matter is that a greater degree of distention of the alveoli is accomplished with 20 mm. Hg inspiratory pressure over a duration of 3.5 seconds, as shown by a tidal volume of 3,700 cc., than is achieved by a 40 mm. Hg inspiratory pressure when applied for 2 seconds, which results in a tidal volume of 3,200 cc. in the same subject. With an E.W.N.P. apparatus recently tested, the time for inspiration was set at 2.0 and 2.5 seconds with an inspiratory pressure of 20 mm. Hg; the resultant tidal volumes were 2,900 and 3,500 cc. in the same subject. However, the expiratory flow rates are substantially increased when the inspiratory pressure is raised from 20 to 30 mm. Hg, with inspiration time 2.0 to 2.5 seconds.

In patients with pulmonary emphysema the technic of application of E.W.N.P. is of consid-

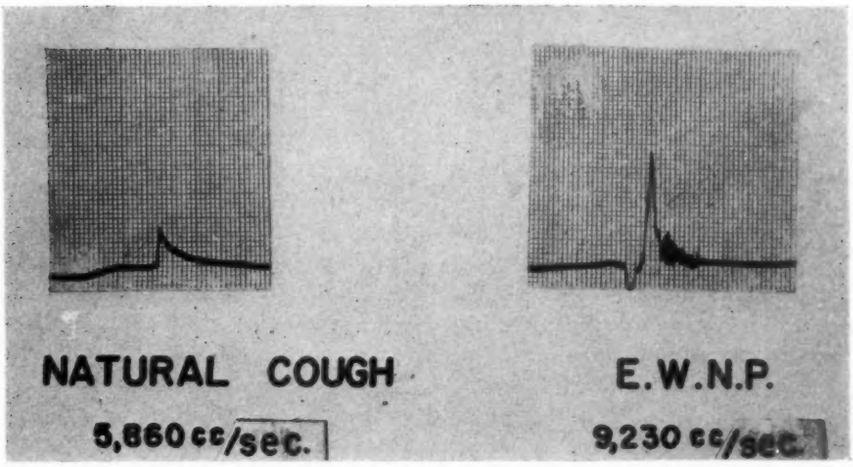

FIG. 5. The maximal cough in a patient with mild pulmonary emphysema resulted in a moderately high flow rate, 5,860 cc. per second. It was further increased with the use of E.W.N.P. to 9,230 cc. per second.

erable importance. The patient should be instructed not to inspire by a voluntary effort nor to blow out or cough during expiration. The volume of the air entering the lungs should inflate the chest; inflation of lungs by applied air pressure alone prevents the inspiratory musculature from being maintained in a state of contraction at a time when abrupt deflation of the lung has been instituted. In a recent survey of thirty clinic patients who had not been taught the passive method of lung inflation, 30 per cent revealed a complete failure in respect to the demonstration by the pneumotachygraph of high expiratory flow rates; in some, continued inspiration was evident even after the tripping of the solenoid valve had developed an expiratory flow rate of 10 L. per second at the mouthpiece.

In patients with myasthenia gravis, poliomyelitis and other neurologic disorders the maintenance of undue inspiratory contraction of the muscles of respiration naturally does not take place and effective elimination of retained mucopurulent sputum is readily obtained.

When lung inflation has been satisfactorily accomplished, expiration is initiated at a predetermined time interval, with a sudden exposure of the upper respiratory passageway to a negative pressure of 40 mm. Hg and to a current of air from a motor blower unit that has the capacity to produce a negative or suction flow of 10 L. per second. Expiratory flow rates measured at the mouth of between 6,000 and 10,000 cc. per second have been found effective in promoting the movement of retained pulmonary secretions from the smaller bronchi into the upper respiratory passageway. In cases of pulmonary emphysema low and ineffective flow rates are characteristically produced in their natural cough.

Patients with pulmonary emphysema have been observed in whom substantial increase in the vital capacity has taken place even when little expectoration has followed its use. It may be mentioned here that although bronchial secretions are frequently brought into the mouth in patients with neurologic disorders, the use of E.W.N.P. in pulmonary emphysema is followed by a gradual movement of retained mucus into the upper respiratory passageway after a series of treatments and then expectorated by a slight or moderate coughing effort of the patient.

As seen in Figure 5, the cough of maximal effort of the patient with mild pulmonary emphysema resulted in an expiratory flow rate at the start of expiration of 5,860 cc. per second as compared to a flow rate of 9,230 cc. per second produced by E.W.N.P. In severe cases of emphysema maximum expiratory flow rates in vigorous coughing are frequently below 3,000 cc. per second. Deflation of the chest takes place swiftly during the negative cycle, with a marked (6 cm.) rise of the diaphragm into the chest and a marked shortening and narrowing of the bronchial tree. The pressure drop of 60 to 70 mm. Hg within the mask is initiated, as mentioned heretofore, at a time when the bronchial tubes leading to the bullous

as well as to the more normal areas of the lung are widely dilated; the kinetic current of air thus produced may not only move secretions outward but also may deliver air from the more diseased as well as the more normal parts of the lung in a way not accomplished by forceful expiration of the patient.

Other forms of pressure that have been applied by the patient himself in the treatment of pulmonary emphysema may be briefly mentioned. Manual compression of the chest and upper abdomen, as indicated previously, represents a form of positive pressure applied to the thorax comparable to negative pressure applied to the upper respiratory passageway. In pursed-lip breathing air is slowly forced through constricted lips; in essence this is a type of expiratory pressure breathing. The head-down position makes use of the pressure of the viscera on the diaphragm, which results in a conspicuous relief of dyspnea and an equally marked fall in pulmonary ventilation. Any procedure which applies an upward pressure on the diaphragm or decreases the downward pull of the viscera on the diaphragm in effect aids the relaxation pressure of the lung. The gorilla posture is of value to patients with pulmonary emphysema because it tends to prevent some of the physiologic handicaps induced in part by the erect posture, i.e., hyperventilation of the periphery of the lungs, especially at the apices, which is produced by the upward and outward movement of the upper five intercostals, the shoulder girdle and the neck muscles. With diaphragmatic breathing the basal portions of the lungs as well as those near the hilum appear to be ventilated with a markedly more efficient diffusion of oxygen and carbon dioxide. Methods which increase the intra-abdominal pressure permit the diaphragm to assume a more convex shape as it extends into the chest, thereby promoting a favorable type of selective (lower lobe and hilar) pulmonary ventilation; this effect has been produced by pneumoperitoneum and abdominal belts.

Although these patient-applied procedures are presented in more detail in discussions of breathing exercises,[11,23–25] some of the physiologic features of the induced changes of the forces in action between the thorax and lungs deserve comment to complete this discussion of the effects of pressure.

Physiologic effects of pursed-lip breathing conducted in the manner described include an increase in bronchial diameter during the expiratory cycle and an increase in peripheral venous pressure.[11,12] Sibilant and sonorous rales frequently clear during its use. This exercise reduced dyspnea during periods of exercise; in patients with latent or overt cardiac insufficiency, pulmonary congestion may be prevented by the induced, voluntary applied increased intrapulmonary pressure, which may in part explain the relief of shortness of breath following exertion. Pursed-lip breathing has, in fact, been effective in terminating acute pulmonary edema in a hypertensive patient in whom previous use of the expiratory pressure mask was equally effective. With the employment of the procedures, the coughing of pink frothy fluid gradually stopped in twenty minutes.

The physiologic basis of instituting increased diaphragmatic motion is that when the thorax is tilted toward the head, the increase in diaphragmatic excursion from 3 to 5 cm. results in a more efficient alveolar gas exchange and a decrease of pulmonary ventilation of approximately 25 per cent.[25] This ventilatory response is in itself a simple reliable test for the presence of anatomic pulmonary emphysema, perhaps superseding in value the comparative decrease in pulmonary ventilation shown by inhalation of 100 per cent oxygen as contrasted to air. Since the arterial oxygen saturation and pCO_2 are either increased or unchanged in the presence of the lowered minute volume of respiration, the ventilatory equivalent, cubic centimeters of oxygen consumed per unit of ventilation, is remarkably increased by the upward visceral pressure, a circumstance that led us to add a new term, viscerodiaphragmatic breathing, in the training practice of patients.[25]

The minute volume of breathing is decreased to a variable extent as the posture of the patient changes from an erect sitting position to a 45 degree forward-leaning posture. As seen in Figure 6, a slight decrease in pulmonary ventilation occurred, from 10,930 to 10,665 cc., accompanied by an increase in the gas volume of the lungs, in this instance 215 cc. The relaxation pressure of the lungs, or the recoil pressure of the lungs, is increased 7 mm. Hg when the downward pull of the viscera on the diaphragm is diminished by a change from the standing to the supine position.[26] The vital

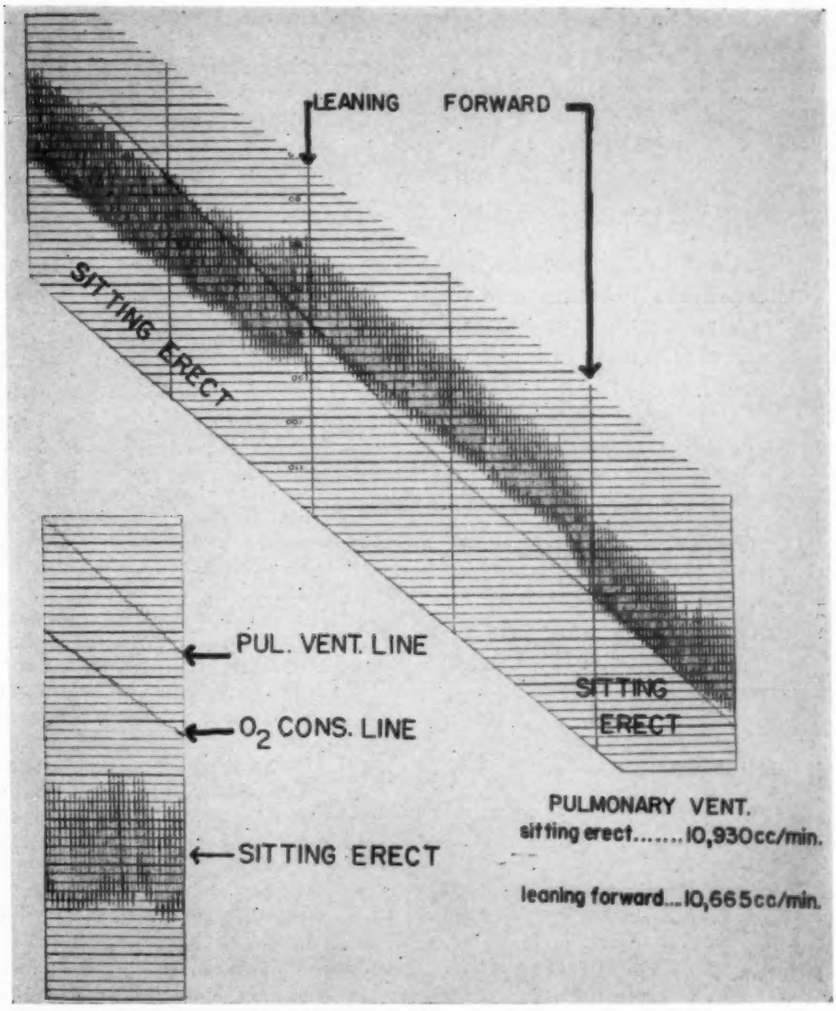

FIG. 6. Leaning forward resulted in an increase of lung volume of 215 cc. and a slight decrease in pulmonary ventilation.

capacity and maximal breathing capacity are either unchanged or lowered in the head-down, supine or leaning-forward positions, which indicates the limitations of these tests in estimating the clinical improvement and more efficient ventilation induced by diaphragmatic respiration. The disadvantageous effects of the erect military posture, either sitting, standing or walking, include hyperinflation of the lung and a downward pull of the viscera which diminishes the retracting force of the lungs. Breathing and postural exercise appears to have a valuable effect in the development of the capacity for moderate exertion.

SUMMARY

The physiologic problems encountered by patients with pulmonary emphysema have been discussed with special reference to application of various types of pressure. The functions of supra-atmospheric pressure breathing, continuous or intermittent, were considered to be in the main: (1) maintenance of a larger diameter of the small bronchi, which is an aid in ventilation in obstructive dyspnea; (2) a retarding influence on the inlet of blood into the heart and lungs, the degree of which is dependent on the mean applied intrapulmonary pressure, whether achieved by continuous or intermittent administration. Use has been made of this circulatory response in the treatment of pulmonary edema and pulmonary congestion. Pursed-lip breathing, a form of expiratory pressure breathing, is at times adopted by the patient and to a limited extent may fulfill both purposes. The employment of

positive-negative pressure breathing in resuscitation has the advantage of a nearly normal mean pressure, and is therefore indicated in patients in shock who require mechanical ventilation. Exsufflation with negative pressure, a form of positive-negative pressure breathing, is characterized by the production of high expiratory flow rates. Its function is that of aiding elimination of retained bronchial secretions but other effects may include an increased delivery of air from bullous parts of the lungs. The mean ventilatory pressure of E.W.N.P. may be adjusted to a negative (subatmospheric) or a positive (supra-atmospheric) pressure, depending upon the length of the negative pressure cycle.

Some of the effects of viscerodiaphragmatic breathing on the pressure relationships between the lung and its surrounding frame of thorax and abdomen are discussed, especially in respect to the decrease in pulmonary ventilation and dyspnea which is induced in patients with pulmonary emphysema.

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Rationale of Pneumoperitoneum in the Treatment of Emphysema

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SUCCESS or failure of any therapeutic measure is predicated, first of all, upon correct diagnosis. It is therefore necessary to point out that the subject of this text is so-called hypertrophic emphysema. Before resorting to any form of treatment of this condition it is mandatory to differentiate it from clinical entities with similar symptoms, and also to recognize the fundamental differences between this disease and senile emphysema. A table illustrating the divergent characteristics of these two lung conditions was given in a previous publication. Briefly, so-called hypertrophic emphysema is a chronic pulmonary disease while senile emphysema is an involutional state, a degenerative process associated with advanced age.

The essential physiopathologic substrate of so-called hypertrophic emphysema is composed of three deviations from normal. These are: (1) bronchoalveolar changes, (2) muscular disturbances and (3) cardiovascular alterations. Intelligent, purposeful therapy should aim at their correction or amelioration.

Bronchoalveolar changes are noted in the form of distention, destruction and confluence of alveoli and in the form of stenosis or occlusion of bronchi and bronchioles either by spasm or by fibrosis or both. It is not irrelevant from the viewpoint of applicability of artificial pneumoperitoneum or any other method of treatment to recognize chronic, excessive cough as the principal factor in the etiology of emphysema. It is known that during the process of coughing the intrapulmonary pressure is increased. Compressed air contained in the lung is the expulsive medium which is instrumental in the removal of inflammatory exudate or other material from the air passages. The degree of pulmonary pneumatic hypertension during cough depends upon the force exerted by the expiratory muscles (rectus abdominis, the external and internal oblique and transverse abdominal, and also, the internal intercostal muscles). During a severe coughing spell the intrapulmonary pressure may rise to 200 mm. of mercury over and above atmospheric pressure. Cough as a reflex mechanism is a useful defense reaction of the body; nevertheless, even under the best of circumstances it represents undue stretch and strain upon the alveoli and the elastic elements of the lung. When this aerodynamic trauma is intense, frequent and protracted enough, its detrimental effect is inevitable.

Destruction of the alveoli and elastic elements of the lung inexorably follows chronic, severe, uncontrolled cough. The deleterious influence of cough upon these structures depends not only upon the severity of cough but also upon the pathologic conditions which are the incentive causes of cough and also upon the age of the patient. When as the consequence of infection the vitality of the lung tissue is impaired, or because of diminished blood flow through fibrosed vessels the nutrition of these tissues is below par, they become more vulnerable to the destructive force of tussic aerodynamic trauma. For an expedient orientation in the management of so-called hypertrophic emphysema, therefore, the role of cough as the most important causative factor must be accepted. At the same time it is well to remember that emphysema in itself may provoke cough. Emphysema leads to hypoxia. Hypoxia, in turn, results in increased irritability of the sensory nerve endings of the bronchial mucosa and thus induces more cough. Obviously this situation represents a vicious circle which if not broken may have grave consequences.

The alveoli are the specific end points for oxygen uptake and for the elimination of carbon dioxide. Extensive destruction of alveoli interferes with the normal respiratory function of the lung. The loss of alveoli and the consequent respiratory insufficiency are aggravated by the disappearance of the elastic elements of the lung. Because of the latter a functional deficiency develops in the lung as well as in the

muscles of the thorax, including the diaphragm. The elastic elements exert a constant centripetal (hilusward) traction. The centripetal traction is responsible for the expiratory contraction of the lung. With pronounced loss of the elastic elements, expiratory hilusward recoil of the lung is greatly reduced or it is entirely absent.

The intrapleural negative pressure is another manifestation of the centripetal traction of the elastic elements of the lung. The intrapleural negative pressure holds the lung in apposition to the chest wall; also, it draws the chest wall inward. This inward pull prevents abnormal distention of the thoracic cage through the force of the inspiratory muscles. Moreover, the suction effect of the intrapleural negative pressure is instrumental in holding the diaphragm at its normal level.

With marked loss of pulmonary elasticity, the thoracic cage is dilated (barrel chest) and the diaphragm occupies a constant, abnormally low position. Both of these changes are of crucial importance relative to pulmonary ventilation and respiration. Normally the centripetal traction of the elastic fibers of the lung is competent to maintain a physiologic and anatomic balance against the combined effect of the gravitational force of the atmospheric air and the outward-pulling action of the inspiratory muscles of the thoracic wall (external intercostal, cartilaginous portion of the internal intercostal, levatores costarum and the superior and inferior serratus posticus muscles). With the loss or pronounced reduction of the centripetal traction—which is associated with a lessening or complete disappearance of the intrapleural negative pressure—the influence of the inspiratory muscles and of the pressure of atmospheric air are unopposed. Consequently, the bony cage of the thorax is distended to an extent its anatomic limitations permit. If this is so, it can be readily appreciated that in this overexpanded condition the inspiratory muscles are unable to attain further distention of the chest wall. Approximately 50 per cent of ventilatory failure in emphysema is explainable on this basis.

Like the inspiratory muscles of the bony cage of the thorax, the diaphragm becomes functionally incompetent in its characteristically low position in emphysema. The serious implications of this positional change of the diaphragm become more obvious if one recalls the site of origin and normal location of this muscle. Its muscular fibers originate from the posterior surface of the xyphoid process of the sternum, from the inner surface of the costal cartilages and adjacent portions of the lower six ribs, from the lumbrocostal arches and from the lumbar vertebrae. During expiration the highest point of the dome of the diaphragm corresponds to the following bony landmarks: in the anterior midline the xyphosternal notch; in the midclavicular line the lower surface of the fourth rib on the right side and the upper surface of the fifth rib on the left side; the level of the angle of the scapula on the right side and 1 inch below the angle of the scapula on the left side; and the level of the spine of the eighth thoracic vertebra. The expiratory rise of the relaxed diaphragm is accomplished by the suction effect of the intrapleural negative pressure. The latter is the same on both sides of the chest. The equality of right and left intrapleural negative pressures assures mediastinal balance. The right pleural cavity being larger than the left, this equilibrium is made possible only by a low position of the right apical region and by a high position of the hemidiaphragm on the right. In this physiologic phenomenon lies the explanation of the hitherto unsolved topographic peculiarity of the right apex of the lung and the higher position of the right hemidiaphragm as compared to the left.

Decrease in or complete disappearance of the intrapleural negative pressure in emphysema permits the gravitational force of atmospheric air to distend the lung. This change together with lack of upward suction are responsible for the characteristically low position of the diaphragm. In advanced cases of emphysema the diaphragm may be found from 5 to 10 cm. lower than its normal position. Because of this further inspiratory descent may be slight or entirely absent. I have noted in a number of instances twitching of the diaphragm (diaphragmatic athetosis) as an inspiratory equivalent. Functional insufficiency of the diaphragm is a cardinal feature of emphysema. From 37 to 47 per cent of air ventilated by the lung on quiet respiration is accounted for by the cyclic descent and ascent of the diaphragm.

Years of experience have convinced me that artificial pneumoperitoneum is capable of restoring diaphragmatic function in patients with emphysema to an extent which is sufficient to relieve respiratory embarrassment or even

to restore normal physical workability. Pathologic changes represented by extensive destruction of alveoli and elastic elements of the lung are irreversible. Restitution of these tissues is a physical impossibility. This fact means an inherent limitation in the treatment of this disease regardless of the type of therapeutic intervention. Even so, by improving diaphragmatic function one can utilize the remaining intact components of the lung.

Artificial pneumoperitoneum is a simple and safe procedure which can be carried out by physicians of average manual dexterity. Injections of 500 to 800 cc. of air at weekly intervals bring about the desired result. Technical details of this procedure and other pertinent information have been outlined by the author in previous publications. At this time I wish to emphasize the following points concerning artificial pneumoperitoneum:

1. Elevation of the diaphragm is attributable partly to the upward pressure of the air injected and partly to the neutralization of the subdiaphragmatic negative pressure. Elevation of the diaphragm takes place when air occupies the subdiaphragmatic space. Organs normally in apposition to the diaphragm (liver, stomach, spleen) are separated from it (visceroptosis).

2. Under the influence of artificial pneumoperitoneum the intrapleural pressure becomes more negative. This greater negativity draws the diaphragm upward and the chest wall inward. In consequence of the latter, the inspiratory muscles of the chest wall are likely to regain some of their normal function and thus facilitate respiratory excursions of the chest wall. Artificial pneumoperitoneum changes adiaphragmatic respiration into diaphragmatic respiration and simultaneously a dyspneic state into a eupneic one.

3. In consequence of improved ventilatory function, more oxygen reaches the lung and the inhaled air is evenly distributed. The elimination of pulmonary pneumatic dyskinesia (faulty distribution of tidal air) is an important phase of the therapeutic potentiality of pneumoperitoneum. Consequently, oxygen saturation of the arterial blood is increased and its carbon dioxide concentration is decreased. All patients with clinically manifest emphysema live in an inner environment of constant hypercapnia. The latter results in symptoms which may be easily misinterpreted. These include headache, irritability, lassitude, malaise, drowsiness, somnolence, confusion, stupor and coma. Hypercapnia may have a fatal termination. In some extreme instances of hypercapnia artificial pneumoperitoneum may be life-saving.

4. By re-establishing negative pressure in the pleural cavity or by increasing the negativity of the intrapleural pressure, return of venous blood from the greater circulation to the heart is facilitated. This is associated with a lowering of the venous pressure. Exceptions to this rule are attributable to peculiar circumstances—extensive pulmonary damage by loss of specific tissues, diaphragmatic fixation or atrophy, severe cor pulmonale—but they do not invalidate the possible therapeutic benefits of this measure. Increased negativity of the intrapleural pressure reconstitutes the gradient from the right ventricle to the capillaries of the pulmonary artery. The resulting improved circulation in the lung contributes substantially to the correction of abnormal oxygen–carbon dioxide exchange, and at the same time relieves the work of the right ventricle.

5. Increased intraperitoneal pressure attained by pneumoperitoneum causes reflex relaxation of the peribronchial and peribronchiolar smooth muscles. Bronchospasm may be an antecedent, causative factor of emphysema. By partial occlusion of the bronchial lumen, spasm may result in a check-valve mechanism. This permits the inflow and prevents the outflow of air at sites distal to the constriction. The consequent alveolar distention may end in rupture of the alveolar walls. Bronchospasm is a common accompaniment of emphysema. It is due either to coexistent pulmonary infection or fibrosis or to emphysematous changes themselves. In any event, bronchospasm is a liability in that it interferes with the free passage of air current, leads to dyspnea and increases cough irritability.

6. There are two additional coincidental benefits of pneumoperitoneum treatment: (1) alleviation of respiratory fatigue and (2) improvement in the cough mechanism with more forceful expectoration. With the relief from peripheral venous stagnation, reflex constriction of the renal vessels and consequent elevation of systemic blood pressure may be corrected.

Artificial pneumoperitoneum has been used for the treatment of emphysema for more than a quarter of a century. Empiric clinical observations as well as respiratory function

studies attest to its value. Of course it is recognized that it has its therapeutic limitations. In selecting patients for this treatment the following possibilities should be kept in mind as causes of failure: (1) anatomically and functionally irreversible, extensive loss of alveoli and elastic elements of the lung, with intact components insufficient for competent respiration under the best of circumstances; (2) widespread pulmonary fibrosis which not only replaces the major part of the essential elements of the lung but also by its solidity renders the lung virtually rigid and unexpandable; (3) sustained bronchospasm which cannot be alleviated by appropriate measures; (4) diaphragmatic adhesions which result in fixation of this muscle and render its elevation impossible; (5) atrophy of disuse of the diaphragm is a grave sequel of long-standing emphysema; at this stage the diaphragm is functionally useless; (6) heart failure which cannot be corrected; and (7) uncontrollable complications which interfere with cardiorespiratory function.

CONCLUSIONS

An analytic assaying of the pathogenesis and pathologic physiology of so-called hypertrophic emphysema points toward restoration of the normal position and function of the diaphragm as an expedient therapeutic measure. Clinical observations and results have vindicated the postulate that artificial pneumoperitoneum is a serviceable treatment of this disease.

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Advances in Inhalational Therapy in the Management of Diseases of the Chest

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THE knowledge of the physiopathologic mechanisms responsible for the sequence of events that occurs in the patient with bronchial asthma and pulmonary emphysema is necessary for the correct management. The patient with intractable bronchial asthma usually presents a picture of marked physiologic imbalance. Evidence of hypoxia, cyanosis, dehydration, drug intoxication, disturbed psyche and peripheral vascular shock is usually observed.[1] Further disturbances may be noted because of the changes induced by the widespread use of the antimicrobial agents, hormonal and oxygen therapy. In fact death may come from any of these enumerated factors. Formerly death was more commonly due to asphyxia, resulting from the plugged bronchi and bronchioles, oversedation or to the failure of endogenous discharge of adrenal hormones which are necessary in the defense mechanism against stress.[2]

The patient with chronic pulmonary emphysema is afflicted with a diffuse, progressive, obstructive and hypoxic type of chronic emphysema in which pathologic distention of alveoli has persisted for some time.[3] This type of emphysema commonly occurs with or as a complication of chronic bronchial asthma, but may be associated with practically all pulmonary diseases, particularly bronchiectasis, serious pulmonary infection, the pneumoconioses, sarcoidosis and tuberculosis. The common denominator appears to be bronchiolar constriction and retardation of expiratory air flow.[3] Clinical manifestations depend upon the degree of pulmonary insufficiency. They may range from coughing, wheezing and shortness of breath on exertion in the early stages to the effects of chronic hypoxia and carbon dioxide retention in the intermediary stages, and to chronic cor pulmonale with heart failure in the final stages.[4] Many patients do not survive to the final stage.

There appears to be an increasing incidence of chronic pulmonary emphysema in this country which may be related directly to the increase in industrial and environmental inhalant vapors, gases, fumes, dusts and tars, or indirectly to the increased incidence of respiratory infections or allergies under these circumstances. These various irritants to the bronchioles produce progressive narrowing and eventually the typical overdistention of the lungs seen in emphysema. This may well be the price we have to pay for our advances in living and in industry.

The various factors responsible—allergic, hormonal, psychic, occupational, infectious, etc.—should be analyzed in every patient. The preventive and therapeutic management of the patient with progressive bronchial asthma, emphysema and/or suppurative disease of the lung all too often requires an "economic prescription" rather than one that can be written on the doctor's prescription pad. Repeated and long periods of hospitalization along with a variety of mechanical breathing apparatus, physiotherapeutic rehabilitation employing diaphragmatic breathing training,[5] antimicrobial and hormonal agents, and the careful use of therapeutic aerosols and oxygen therapy make it possible to prolong life and restore many of these patients to a life of economic usefulness.[3]

This discussion will be limited to only several phases in the management of some of these patients and will include the following:

(1) Therapeutic aerosols: Bronchodilators (adrenergic agents), pamine bromide (anticholinergic agent), pancreatic dornase (pus-liquefying enzyme), cold water vapors (humidity therapy), alevaire® (detergent agent) and dusts of cortisone acetate and hydrocortisone. Equipment for the preceding (air pump and Neb-*EL*izer croup tent apparatus).

(2) Oxygen therapy: Reactions to the use of

oxygen; the carbon dioxide intoxication syndrome—respiratory acidosis.

(3) Pressure breathing therapy: Intermittent positive pressure breathing—inspiratory (IPPB/I); alternating positive-negative pressure breathing (P and N).

THERAPEUTIC AEROSOLS

Bronchodilator Aerosols. Aerosols of the proved sympathomimetic drugs, vaponefrin (2.25 per cent racemic epinephrine) and isuprel® 1:200 (dihydroxyphenylisopropylaminoethanol) are of great value for the relief of bronchospasm and in expectoration. Our laboratory studies employing the protection study technic revealed that isuprel offered the best protection against the effect of acetylcholine; and vaponefrin the best against the effect of histamine.[6] As little as approximately 0.05 to 0.10 cc. of these preparations, nebulized by two to six compressions of the hand bulb of the vaponefrin nebulizer may abort or relieve a mild bronchospastic episode. The relief, however, may be short-lived. Treatments should not be repeated more often than hourly intervals. This technic has replaced to a large measure the use of epinephrine with the hypodermic syringe. More severe bronchospasm may require 0.5 to 1.0 cc. nebulized by continuous flows of oxygen.[7] A Y-tube or simple button-like opening into the oxygen or air feed line allows interruption of aerosol production during expiration. This treatment generally requires ten to fifteen minutes when 5 L. per minute flows of oxygen are employed. We have recently used the simple, portable Eliot Air Pump unit* for the production of continuous aerosols of all types. It requires an A-C outlet for electric power and does away with the need for the oxygen tank and regulator. The air flow rate can be adjusted by a simple turn of an air jet valve to the requirements of the therapeutic agent (rate of delivery cc. per minute). The bronchodilator aerosols may also be introduced along with intermittent positive pressure (inspiratory), thus obtaining the physiologic advantages of bronchodilatation and improved alveolar ventilation.[8] A useless cough is often converted to a productive one with this therapy.

We have investigated several new adrenergic bronchodilator drugs, particularly dapanone,®* 5 per cent and dylephrin.† These bronchodilator agents are capable of improving the time—vital capacity relationships and maximum breathing capacities of mild and moderately ill patients with chronic bronchial asthma. Dylephrin (2.50 per cent racemic epinephrine plus atropine) has the advantages of an added anticholinergic agent in a stable form. It appears of value in the "wet asthmatic" and in those patients with associated disorders, particularly cardiac asthma.

Fortunately, refractoriness to any one of these preparations apparently is not immediately passed on to the others. The individual toxicities and degrees of pressor response should be noted by the physician and patient in selecting the preferred drug. Clinically one patient's asthma frequently responds better to one of these drugs than the other. The reverse order of efficiency may be true in the same patient at another time.

Pamine Bromide Aerosols. It was suggested that the combination of a good antihistaminic and a good anticholinergic drug with bronchodilator properties would be a most ideal therapeutic agent in bronchial asthma.[1] Parasympatholytic agents, particularly atropine, scopolamine and bellafoline have demonstrated excellent anticholinergic protection in our laboratory.[9] The mild central sedative effects of these alkaloids on the mucous membrane of the tracheobronchial tree may lead to further inspissation of the already semi-solid plugs, making coughing and their expulsion more difficult.

We have employed aerosols of pamine®‡ (epoxytropine tropate methylbromide), an anticholinergic agent for the relief of bronchospasm.[10] Doses of 0.33 mg. dissolved in 1.0 cc. of saline or distilled water were employed with the direct nebulizer-oxygen technic and also with the nebulizer-IPPB/I-Bennett unit valve. In a series of thirty-four patients with mild chronic bronchial asthma an average improvement of 300 cc. in the vital capacity was noted after treatment with 1 cc. pamine aerosols [10] The average improvement, though lower, com-

* Manufactured by Eliot Medical Plastics, Inc., Lynn, Mass.

* Kindly supplied by Sharp & Dohme, Inc., Philadelphia, Pa.

† Kindly supplied by Irwin, Neisler and Company, Decatur, Ill.

‡ Kindly supplied by the Upjohn Laboratories, Kalamazoo, Mich.

pares favorably with that noted with several adrenergic aerosols studied in a similar group of patients in our laboratory.[11] No side reactions were observed with pamine aerosols.

In a series of gastric antisecretory compounds under investigation pamine was found to be one of the most effective adjuncts with the least troublesome reactions.[12] Anticholinergic aerosols such as pamine may be of some value in the depleted sick asthmatic who is hypotensive and sweating profusely and may be considered to exhibit a systemic picture of parasympathetic stimulation. We are presently exploring the advisability of combining pamine with an effective antihistaminic or adrenergic aerosol.

Pancreatic Dornase Aerosols (Pus Lytic Enzyme). In the presence of bronchial infection, bronchiectasis or viscid, tenacious, mucopurulent secretions, the use of a new pus-liquefying enzyme, pancreatic dornase,* as a therapeutic adjuvant may be most helpful.[13] The harmful potentialities of these secretions by obstructing airways and acting as a culture medium for infectious microorganisms is recognizable. The rapid and safe evacuation of these secretions in the simplest possible manner is a problem of great importance. The use of dornase prior to and after lung operations in asthmatic patients may make it safer for the thoracic surgeon and may furthermore increase the patient's chances for a more prompt recovery, freer of complications which may be crippling or even fatal.

Pancreatic desoxyribonuclease (pancreatic dornase) is prepared from beef pancreas. Desoxyribonucleoprotein is an important constituent of purulent exudate and it determines the character, viscosity and amount of sediment of such exudates.[14] Desoxyribonuclease, whether of streptococcal origin (streptodornase) or of pancreatic origin (pancreatic dornase) is a pus-liquefying enzyme and is capable of degrading desoxyribonucleoprotein.[15,16] The action of pancreatic dornase is primarily one of depolymerization and but little degradation of desoxyribonucleoprotein occurs.[17] The absence of appreciable amounts of noxious degradation products, which might be absorbed systemically, permits its relatively safe use. We have not observed any side effects in our preliminary series of treated patients. Nevertheless, because of the protein nature of pancreatic dornase allergic reactions should be watched for in allergic or previously sensitized subjects. Usually one may observe decreased viscosity of sputum, greater ease of expectoration and a more productive cough, then gradual diminution, and finally, following the evacuation of secretions, less bronchoconstriction.

We have employed dosages of 50,000 to 100,000 units per treatment, one to three treatments daily for one to six days as a full course of therapy. Clinical improvement, decrease in cough and volume of sputum may be used as a therapeutic guide for dosage and continuation of therapy. The dornase is mixed with 1 or 2 cc. of a buffer solution (Sorenson) or saline shortly before its administration. One cubic centimeter of a potent bronchodilator aerosol should be added to the mixture when bronchoconstriction is evident. The pancreatic dornase solution is aerosolized with the direct vaponefrin nebulizer-oxygen flow technic,[7] or with the nebulizer-Eliot air pump unit or with the intermittent positive pressure-nebulizer-Bennett valve unit.[8] The air or oxygen flow rates should be kept at 4 or 5 L. per minute flow to avoid foaming in the nebulizer.

Continuous Aerosol Therapy with Cold Moist Air and/or Alevaire. There is suggestive evidence that infection of the respiratory tract may depend upon changes in the physiology of the respiratory tract itself. The high incidence of upper respiratory infections in our New England states in the late fall and winter months may be precipitated in large part by the hot, dry air present in homes and offices, tending to dry the lung tissues to some extent. This change in pulmonary physiology may predispose to infection. This is a particular problem in the management of recurring bronchitis, especially in asthmatic children and to a lesser extent in the adult patient with chronic sinobronchitic disease, asthma and emphysema, in whom the allergic hunt has not been revealing. The bronchitic attack frequently triggers a bout of asthma and generally is responsible for the intractable course, particularly in the adult group.

Humidification therapy should be considered in the treatment of these patients.[18] The use of the steam kettle and the high humidity steam room is an archaic mode of achieving such therapy. Unfortunately, it is not relatively

* Kindly supplied by Sharp & Dohme, Inc., Philadelphia, Pa.

simple to attain nearly 100 per cent water-vapor saturation in an environment of about 70°F. (or slightly lower). Even when this is achieved at the oropharynx, the inspired air enters the bronchial tree where the temperature is 90°F. or above (with fever). The air must not only be fully saturated, but also contain fine moist droplets to ensure the high percentage of humidity as it passes into the lungs.[19]

The continuous administration of cold water vapors or non-toxic detergent aerosols (alevaire) is most effective therapeutically when introduced into enclosed oxygen tent units. The therapeutic objectives are the following: first, high humidity; second, stability of small particle size aerosols; third, adequate cool-temperature control within the tent; and fourth, prevention of "raining out" on the patient or in the tent due to the formation of loose droplets of moisture when the humidified, moisture-laden air becomes rapidly dehumidified by impact with cold currents of air.

We have found the Neb*EL*izer-Permatent croup apparatus* simple, practical and convenient for prolonged nebulization of cold water vapor or alevaire.[20] The Neb*EL*izer apparatus* produces a continuous fine fog of water or alevaire, originating from the attached 500 cc. reservoir of solution.[21] The patient's head is placed in the enclosing transparent plastic Permatent unit. A single oxygen tank and regulator set at flows of 12 L. per minute, attached to the special adaptor of the Neb*EL*izer, insures continuous nebulization, without "rain outs" of large particles onto the patient. Water vapor saturation over 90 per cent, temperatures below 70°F. and oxygen concentrations between 40 and 50 per cent can be obtained quickly and maintained comfortably within the tent with this technic. When employed as a home croup unit the Neb*EL*izer can be attached directly to the ABC plastic face tent* or to the O.E.M. meter mask.† The air pump unit may be substituted for the oxygen tank when intermittent therapy for periods up to twenty to thirty minutes are considered satisfactory. The oxygen nipple feed, which is marked for the Permatent entrance, is closed off with this technic and the flow rates may then be reduced one-half.

Employing alevaire* (triton, sodium bicarbonate, glycerin) we generally advise 100 per cent concentrations with alternating cold water vapor therapy—500 cc. of each. Alevaire helps to lower the surface tension of the adherent mucopurulent secretions and may thus act as a cleansing agent. This has proved most helpful in the management of troublesome bronchitis in small children and adults. Therapy may be continuous for one or more days or intermittent as needed. We have not observed any toxic effects from alevaire therapy. However, in the enfeebled patient, unable to expectorate freely, the adequate use of repeated tracheal catheter aspirations or, when available, the use of exsufflation should be resorted to, in order to prevent the literal "drowning in their own secretions" which may be noted in some of these patients.[22,23]

We have employed dusts of cortisone acetate and hydrocortisone, cortef† acetate and emulsions of hydrocortisone, for topical nasal therapy in some of the patients treated in this series during periods when they were not receiving any other form of hormonal therapy. A total of eighty-two patients were treated with either cortisone (thirty-seven patients) or hydrocortisone (forty-five patients) dusts. Their complaints centered about the following: seasonal hay fever, perennial vasomotor rhinitis, nasal polyposis, recurring sinobronchitis and the common cold. The cortisone acetate was prepared in a 5 mg. capsule and the hydrocortisone acetate in a 15 mg. capsule. The gelatin top of the capsule was removed and the bottom part of the capsule filled with the powder was seated in the Upjohn plastic powder inhaler. The nasal tip was placed into the nares and the patient instructed to sniff deeply and slowly while squeezing the bulb. When there was evidence of marked nasal obstruction, each treatment was preceded by spray or displacement therapy with an effective nasal vasoconstrictor to insure more successful deposit of the dust. The patients were permitted to take two or three sniffs into each nostril at one to two-hour intervals as needed. The majority of the patients (72 per

* Manufactured by Eliot Medical Plastics, Inc., Lynn, Mass.

† Manufactured by O. E. M. Corporation, E. Norwalk, Conn.

* Kindly supplied by Winthrop-Stearns, Inc., New York, N. Y.

† Kindly supplied by The Upjohn Company, Kalamazoo, Mich.

cent) noted some relief from itching, cessation of rhinitis, lessening of the postnasal drip and relief from headaches. These effects were but short-lasting in most applications. Nevertheless, they were considered of some definite topical value. There were no systemic effects noted and the main side effect was "caking of the nares" in some patients. Even this appeared better tolerated than the rhinorrhea in some. On the whole the better results were observed in the patients treated with hydrocortisone acetate dust. A hydrocortisone emulsion, 15 mg. per cc., was tolerated fairly well when employed in the form of continuous nasal nebulization, using 1 cc. with the vaponefrin nebulizer-nasal tips-oxygen technic and usually gave adequate relief from the associated nasal obstruction. An interesting trial with hydrocortisone dust aerosols was made in seven patients with severe common colds during the winter months. Five described reduction in the manifestations and duration of their "colds" (rhinitis) and nasal obstruction and sinus pain. Two patients had no benefit. Further studies with combinations of antihistaminic and hydrocortisone dusts in similar problems are under way. The absence of systemic effects with this form of therapy, employing these particular drugs, and their peculiar anti-inflammatory properties at the shock-organ-nasal site would indicate their possible usefulness in the aforementioned types of patients. This may serve as a boon to hay fever subjects and may permit smaller systemic dosage with hydrocortisone or hyposensitization therapy during seasonal treatment.

OXYGEN THERAPY

The seriously ill patient in status asthmaticus is suffering from the effect of diffuse respiratory obstruction and secondary hypoxia. When there is evidence of hypoxia and cyanosis, the patient should be given oxygen. His physical and personal requirements, as well as the concentration of oxygen desired, should be considered in selecting the type of equipment to be used.[1] Unfortunately, most patients in status asthma tolerate poorly the tight-fitting rubber face masks which are necessary when concentrations of oxygen above 60 per cent are indicated. The newer types of "iceless" refrigeration tent units are comfortable and effective means of administering oxygen in concentrations of 40 to 60 per cent. However, they involve costly apparatus and maintenance. The Permatent apparatus[24] has proved ideal for routine ice tent–administered oxygen and permits average concentrations of 50 to 60 per cent with temperatures below 70°F. The simple ABC Plastic Face Tent[25] supplies average concentrations of 50 per cent oxygen in the inspired air with oxygen flow rates of 6 L. per minute. The patients do not complain of claustrophobia or a sense of suffocation.*

In general, there has been an overemphasis on the danger of inducing the carbon dioxide intoxication syndrome and respiratory acidosis by the sudden administration of high concentrations of oxygen in patients with classic intractable bronchial asthma. This danger, however, is always present in patients with chronic hypoxia, secondary to chronic pulmonary emphysema or chronic pulmonary heart disease, particularly if respiratory-depressing drugs are administered preceding or along with the high concentration of oxygen.[3] In these patients the nasal catheter-humidification technic is best employed. Initial low concentrations of about 30 per cent with flow rates of 4 L. per minute should be used. The flow rates may be cautiously increased by daily increments to 6 L. per minute and subsequently the therapy may be maintained more simply and safely with the ABC Plastic Face Tent.

The medullary respiratory centers in these patients appear to have lost their sensitivity to the pCO_2 stimulus for respiration (centrogenic drive). The chemoreflex drive for respiration (the hypoxic stimulus from the sensory nerve ending in the carotid and aortic bodies) is then mainly responsible for maintaining respiration. The sudden injudicious relief of hypoxia may be followed by a breakdown in the homeostatic mechanisms sustaining respiration, and further hypoventilation may ensue. The carbon dioxide retention usually brings about a compensatory increase in the alkali reserve (metabolic alkalosis) and a fall in serum chlorides and increase in urine chlorides. Greater increase in the arterial pCO_2 and content may follow, and ultimately respiratory acidosis, with a drop in arterial pH. These factors appear primarily responsible for producing weakness, headache, air hunger, neurologic

* An analysis of alveolar ventilation reveals that for most pulmonary patients an oxygen concentration of 30 per cent is sufficient for normal arterial blood saturation.

manifestations, drowsiness, coma, delirium and death, which may develop progressively under such conditions.

This troublesome syndrome should not occur if one does not further depress respiration by the use of the respiratory depressing drugs (e.g., morphine, barbiturates, anesthetic agents) and if the sudden administration of high concentrations of oxygen to the chronically hypoxic patient is avoided.[4]

Should respiratory depression occur following the administration of one of the opiate respiratory depressing drugs or demerol,® intravenous nalline® (N-allylnormorphine hydrochloride) is the antagonist of choice.[26,27] Five to ten mg. injected intravenously followed by a slow drip of 10 mg. of nalline in 1,000 cc. of glucose in water will, as a rule, increase ventilation promptly. This remarkable "opiate antagonist" should be in the doctor's bag at all times.

A carefully graded program of oxygen therapy should be employed in these patients,[28] consisting of daily increases in concentrations at the beginning of therapy and a gradual daily reduction toward its cessation. At the outset one should employ flows of 1 L. per minute with the nasal catheter-humidified oxygen technic. The flows may be increased 1 L. daily until 6 L. per minute flows of oxygen are obtained.[28] A concentration of 38 per cent oxygen in the inspired air can be obtained at this flow. Some variations in the flow rates may be necessary from time to time.

A very gradual reduction in the pulmonary ventilation may follow this therapy. This slow change in ventilation permits the progressive development of further compensatory metabolic alkalosis, and prevents a sudden drop in arterial pH. There may also be observed a gradual rise in arterial pCO_2 and CO_2 content. However, following this rise the CO_2 levels may fall, as alveolar ventilation returns to normal. The sensitivity of the medullary respiratory center to pCO_2 may be restored with a graded oxygen program.

The treatment of respiratory acidosis[3] has been summarized in Table 1, and centers about (1) the use of preventive measures, (2) etiologic considerations and finally (3) symptomatic measures to improve ventilation and oxygenation. The zealous physician, affording relief from dyspnea with "adequate" sedation and "treating" hypoxia with oxygen concentrations about 50 per cent, will encounter this syndrome all too frequently in patients with chronic hypoxia secondary to chronic pulmonary emphysema and pulmonocardiac disease. The most important aim in the treatment of respiratory acidosis is to improve ventilation, for only by doing so can one rid the blood and tissues of the accumulated excess of carbon dioxide, and permit the respiratory centers of the medulla to regain their normal sensitivity. Emergency treatment should center about one or more of the following measures: The use of IPPB/I with Bennett valve, employing 30 per cent concentrations of oxygen and bronchodilator aerosols, the use of respiratory body chambers (Emerson and Drinker types), institution of pneumoperitoneum, the graded program of oxygen therapy just described, and finally etiologic therapy when indicated. These measures may be life saving when employed early.

TABLE 1

TREATMENT OF RESPIRATORY ACIDOSIS*

1. Preventive (Best Treatment)
   - (a) Early recognition of signs and symptoms
   - (b) Avoid high concentrations of oxygen
   - (c) Avoid respiratory depressing drugs
   - (d) Avoid combination of (b) and (c)
   - (e) Vigorous antimicrobial therapy
2. Etiologic
   - (a) Drug intoxication
     - Opiates—N-allynormorphine
     - Barbiturates—picrotoxin
   - (b) Acute obstruction of airways
     - Bronchoscopy
     - Tracheotomy
3. Symptomatic
   - (a) IPPB/I-Bennett unit
   - (b) Mechanical respirator chambers (Emerson-Drinker units)
   - (c) Emergency pneumoperitoneum
   - (d) Graded program of oxygen therapy
   - (e) Etiologic treatments when indicated

* From Chronic Pulmonary Emphysema. Physiopathology and Treatment by M. S. Segal and M. J. Dulfano. Courtesy of Grune & Stratton, Inc., New York, 1953.

PRESSURE BREATHING THERAPY

Physiology of Pressure Breathing. The effects of pressure breathing on ventilation and circulation have been the subject of considerable discussion in recent years.[29–34,41–43,52] Numerous mechanical devices have been widely employed in a variety of ventilatory disorders.

The positive pressure applied during pressure breathing inflates the lung to a greater extent than normal inspiration, thereby provid-

ing better ventilation, and extensive inspiratory bronchodilation with more uniform ventilation. However, it should always be kept in mind that this form of therapy may produce untoward changes in cardiopulmonary dynamics unless properly employed.

The pressure volume diagram as developed by Rahn, Fenn and Otis[36–38] is especially helpful in the understanding of the mechanics of breathing. This reveals that vital capacity can be increased slightly by inspiratory positive and also by expiratory negative pressure. With high positive and negative pressures the vital capacity diminishes and may finally reach zero at some undetermined point. The residual capacity is much greater with continuous positive pressures because the expiratory muscles are unable to deflate the chest against the pressure during expiration. Furthermore, some 200 to 500 cc. of blood are squeezed out of the lungs by the developed positive pressure, thus adding further to the increase of residual capacity. With breathing at a continuous positive pressure of more than 9 mm. Hg the chest never comes to rest because the patient continuously exerts some expiratory pressure even during inspiration. When breathing against negative pressure the reverse occurs; continuous inspiratory pressure is exerted by the patient in order to prevent the chest from collapsing.

Hence, continuous pressure breathing may increase the work and fatigue of breathing. This disadvantage can be mitigated by the use of IPPB. The latter, however, may introduce the hazard of hyperventilation and acapnia. Cournand and his group[29] have shown a regular rise of pH with concomitant drop of arterial pCO_2 corresponding to an increase in minute volume from 23 to 132 per cent during IPPB/I, depending on the type of mask pressure used. At positive pressures of more than 40 to 50 mm. Hg, air leakage occurs and at pressures of 60 to 100 mm. Hg, the lung ruptures.[38] Extreme negative pressures lead to vasodilation and finally pulmonary hemorrhage. Injury to the lung itself is caused by overdistention,[39] the distention being related to time as well as to the pressure exerted. Hence it would appear that a high pressure applied over a short period of time might be safer than a lower pressure applied over a longer period of time.

Positive pressure may be transmitted into the gastrointestinal tract and lead to distention of the stomach and intestines. This may produce undesirable vagal reflexes following the gastrointestinal dilatation, increased difficulties of expanding the lungs by any means and actual retardation of the venous return by a tense abdomen.

During deep breathing the stroke volume of the two ventricles is different.[40] The increase in intrathoracic pressure during expiration reduces the filling pressure of the right heart and therefore the stroke volume. At the same time the output from the left heart is increased because of increased return from pulmonary circulation.

In IPPB the same mechanism comes into play in reverse fashion, but the decrease of right heart output during rising mask pressure may be made up during the phase of falling mask pressure. The reverse occurs in the left heart but with limitations, because increased output during inspiration with IPPB can be maintained only during short periods (three to five pulses) by displacement of pulmonary blood. If the inspiratory mask pressure is prolonged, the arterial pulse pressure decreases after the initial rise. Thus the variation in stroke volume in the right ventricle is the important part to consider in relation to changes in cardiac output.

The right ventricular net filling pressure during IPPB is decreased during periods of increased intrapleural pressure. The reverse occurs during periods of decreasing intrapleural pressure. Starling's law postulates that the deficit in cardiac output during increased intrapleural pressure can be compensated for during the period of decrease in intrapleural pressure. If the expiratory time is sufficient, compensation may be complete.

Depending on the presence of normal circulating blood volume, existing vascular tone and capacity of reflex vasoconstriction, the peripheral pressure rises with the rise of right auricular pressure, thus reconstituting the venous pressure gradient. The increased peripheral pressure increases the capillary filtration pressure, resulting in water loss to the tissues. It has been shown[41] that positive pressure breathing for thirty minutes at 30 mm. Hg causes a loss of 4 per cent of blood volume to the tissues.

If sympathetic pathways are ineffective, the reconstitution of the venous gradient is greatly diminished or absent and eventually a dangerous decrease in venous return, cardiac output and blood pressure occurs. The same holds true

for hyperactive sympathetic pathways where maximal reflex vasoconstriction has already been utilized.

In order to compensate for the decreased right ventricular output during the inspiratory phase of rising intrathoracic pressure, an ideal mask pressure with the following characteristics has been proposed:[29] (a) Gradual increase to a maximum of 25 cm. H_2O during inspiration; (b) Rapid pressure drop early in expiration with mean pressure during expiration near to zero; (c) Inspiratory time should not exceed expiratory time, thereby allowing as many heart beats to occur during expiration with increased stroke volume as during inspiration.

Maloney et al.[42–44] have repeatedly stressed the advantage of positive and negative pressure breathing in the presence of respiratory failure and/or circulatory embarassment, the IPPB/I type machines causing a decrease in cardiac output which may be very serious. They found that cardiac output and arterial blood pressure varied with the mean airway pressure during the respiratory cycle rather than with any particular wave form.

Present Studies. In our most recent studies with pressure breathing we have employed the Bennett,[3,8] Halliburton, Emerson, M.S.A. and Vent EL Aire units for IPPB/I, the Eliot Exsufflator[23] to simulate the cough mechanism and the Vent EL Aire for positive and negative pressure breathing. Employing a four-channel, direct-writing oscillograph we simultaneously recorded arterial pressures, peripheral venous pressures, mouth or esophageal pressures and pneumotachographic tracings.

Stroke volumes were calculated with Starr's formula[45,46] for direct arterial measurements, this method allowing the calculation of rapid changes in stroke volumes. The stroke volumes of both ventricles during pressure breathing being different, the latter method will probably not give absolute values but should at least give some indication as to the degree and direction of the variation in stroke volume.

The results of our preliminary studies appear to be of interest.* With the exception of the M.S.A. apparatus, all of the IPPB machines employed produce a mask pressure curve of the type III described by the Cournand group. The end of the inspiratory phase occurs when the peak of the mask pressure is reached. The inspiratory time at identical pressure settings may vary considerable from patient to patient and also in the same patient as the duration of IPPB treatment goes on. Figure 1 shows a typical example: mask pressure set at 26 cm. H_2O. At the beginning the mean mask pressure* is 12.15 cm. H_2O, inspiratory time is 1.8 seconds; the expiratory time 1 second; respiratory rate 21, pulse rate 77; venous pressure 11 cm. H_2O; arterial pressure 129/72 mm. Hg at the end of inspiration, and 107/57 mm. Hg at the end of expiration with no change in stroke volume as compared to ambient air breathing. After five minutes of treatment the mean mask pressure has risen to 13.3 cm. H_2O; the inspiratory time is variable from 1.8 to 3 seconds; the expiratory time, 1.4 to 1.6 seconds. The respiratory rate has fallen to 15; the pulse rate has risen to 92. The arterial pressure was 136/80 mm. Hg at the end of inspiration with a reduction of the stroke volume of 7.3 per cent; and 107/65 at the end of expiration with a reduction of stroke volume of 5.8 per cent. The respiratory changes in venous pressure become apparent: 11 cm. H_2O during late expiration—early inspiration and a rise to 13 cm. H_2O during late inspiration—early expiration. After ten minutes of treatment the mean mask pressure is 13.8 cm. H_2O. Inspiration time varies from 2.2 to 2.8 seconds; expiration time from 1.4 to 1.8 seconds; respiratory rate 14; pulse rate 102. Arterial pressures and stroke volume are the same as at five minutes, but the changes in venous pressure now range from 12 to 19.5 cm. H_2O.

Figure 2 demonstrates the physiologic changes in an asthmatic subject after fifteen minutes of breathing with the Vent EL Aire unit.† Mask pressure is set at 26 cm. H_2O, the mean mask pressure has risen from 6.5 to 9.3 cm. H_2O, inspiratory and expiratory time are equal, both having dropped from 2.2 to 1.3 seconds. The respiratory rate has risen from 14 to 22.5 and the pulse rate has fallen slightly

* We gratefully acknowledge the assistance of Dr. R. G. Monroe, Assistant Resident in Medicine, Third Medical Service (Tufts), Boston City Hospital, in assisting in these studies.

* The mean mask pressure has been obtained by planimetric measurement of three to six respiratory cycles according to the formula:

$$\text{Mean Mask Pressure} = \frac{\text{Calibration Factor} \times \text{Area mm.}^2}{\text{"X" Axis mm.}}$$

† Manufactured by Eliot Medical Plastics, Inc., Lynn, Mass.

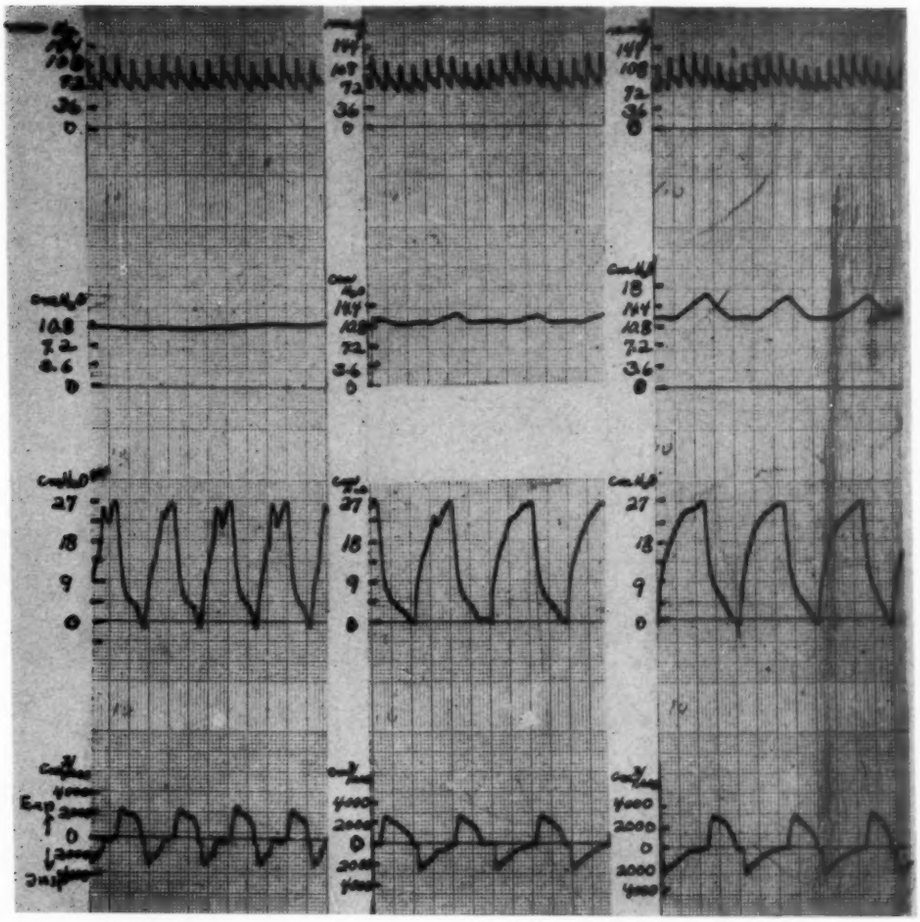

FIG. 1. IPPB/I (Bennett valve) mask pressure at 26 cm. H_2O. After 1′, 5′ and 10′ (left to right) of treatment, recordings from top to bottom are arterial pressure, venous pressure, mouth pressure and pneumotachogram. The paper speed was 5 mm. per second. (Note: inspiration air flow pattern downward, expiration upward.)

from 64 to 60. Arterial pressure recorded during late inspiration-early expiration at the beginning of treatment was 129/86 mm. Hg with an increase in stroke volume of 18 per cent as compared to ambient air breathing, and after fifteen minutes' treatment is 129/93 mm. Hg with a decrease in stroke volume of 3 per cent. The arterial pressure during late expiration-early inspiration was 111/72 mm. Hg with a reduction in stroke volume of 3 per cent and after fifteen minutes' treatment was 122/79 with a reduction in stroke volume of 10 per cent. There was no significant change in venous pressure.

Figure 3 demonstrates the physiologic effects of alternating positive and negative breathing with the Vent EL Aire unit at two different settings for expiratory time. The mask pressure is set at plus 13.5 to minus 12 cm. H_2O; the mean mask pressure for the short expiratory time setting is 2.7 cm. and for the long setting, zero cm. H_2O. The settings were as follows: for the short setting 1.6 seconds inspiratory time and 0.8 seconds expiratory time; for the long setting 2 seconds inspiratory time and 1.6 seconds expiratory time. The arterial pressures vary from 143/86 to 136/100 mm. Hg for the short settings, and from 136/100 to 122/86 mm. Hg for the long settings. The changes in venous pressure vary for both settings from 17 to 19 cm. H_2O; respiratory rate from 27.5 for the short and 17 per minute for the long setting. The stroke volume dropped 30 per cent for the long setting, and 20 per cent for the short setting.

The first forty experiments in six subjects (four normals and two patients with chronic bronchial asthma free of circulatory involve-

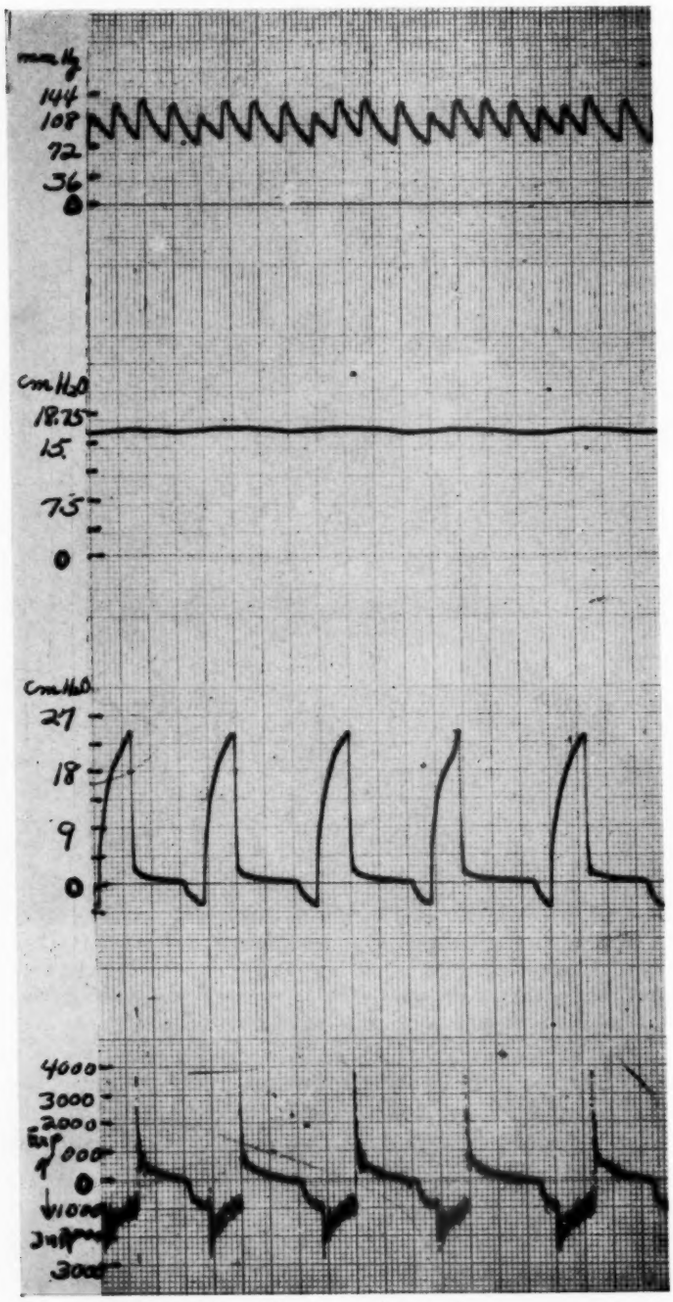

FIG. 2. IPPB/I (Vent EL Aire unit) mask pressure at 26 cm. H_2O. Recorded after 15′ therapy with readings as described in Figure 1.

ment) demonstrated that the influence of pressure breathing on circulation is not only a function of mean mask pressure but also of (1) the absolute time during which the peak pressures are exerted, and (2) the length of treatment. Some of the highest changes in stroke volume occurred in patients who had a mean mask pressure of zero, and some of the lowest changes in patients with mean mask pressure of +12 to +14.

In the course of these studies we were able to demonstrate a significant drop in the pulmonary artery pressure in a patient with chronic pulmonary emphysema by means of IPPB/I The drop became manifest after ten minutes and was striking after fifteen minutes. The

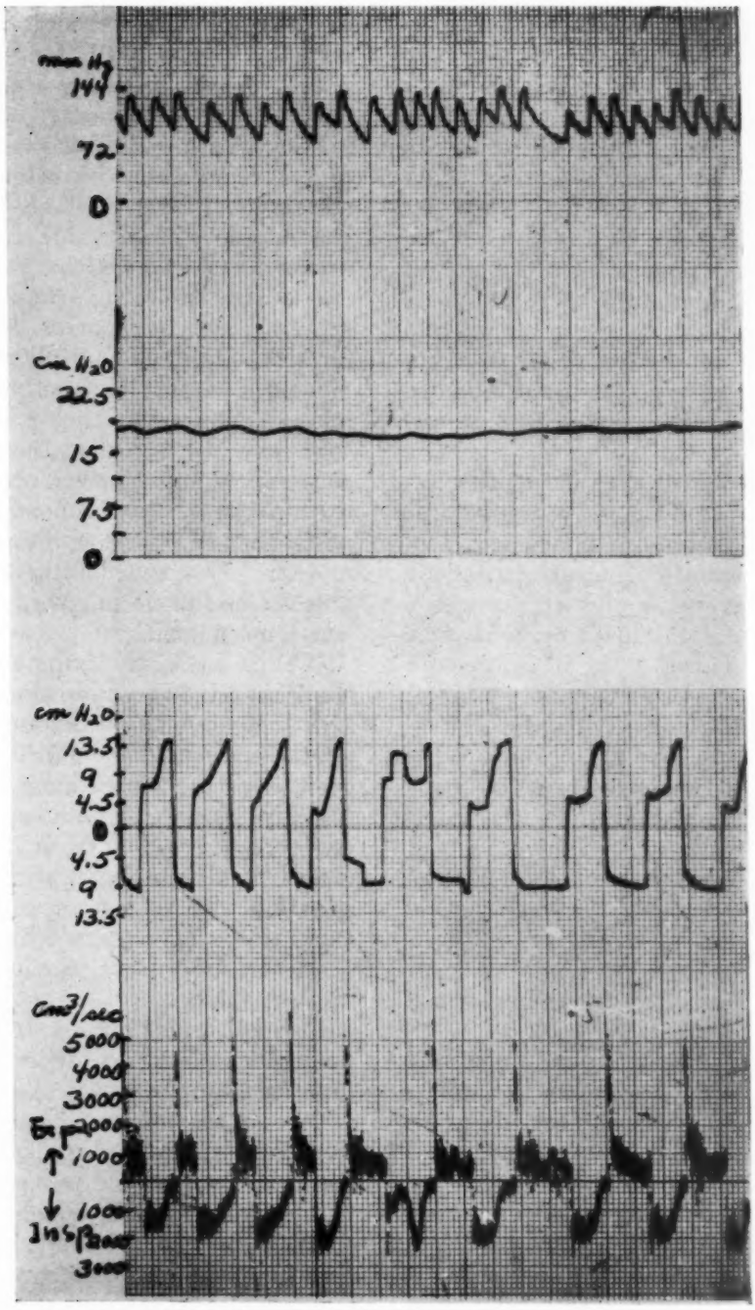

FIG. 3. P and N breathing (Vent EL Aire unit) mask pressures at +13.5 and −10 cm. H_2O. At left, setting for short expiration and at right, setting for long expiration. Readings as in Figure 1.

IPPB/I was administered with the Bennett valve with pressures of 26 cm. H_2O. No simultaneous bronchodilation therapy was employed. Further studies are under way in order to determine how much of the drop is due to the administration of oxygen alone and how much to the IPPB/I.

Clinical Applications of Pressure Breathing Therapy. The application of positive pressure to the airway during the inspiratory phase of respiration (with the use of a mask or mouthpiece), commonly referred to as intermittent positive pressure breathing, may be abbreviated as IPPB/I. The expiratory phase of respiration is entirely passive. The devices usually consist of an inspiratory demand

valve operating on a flow-sensitive or pressure-sensitive principle and require the use of oxygen or oxygen-air mixtures. The more commonly employed are the Bennett, M.S.A., Emerson and Halliburton valves. Positive pressures of 10 to 20 cm. H_2O are usually employed and have been well tolerated. Therapeutic aerosols are generally administered during the inspiratory positive pressure phase of breathing. This type of therapy has found its greatest usefulness in progressive bronchospastic disorders wherein uneven pulmonary ventilation exists, particularly when employed along with bronchodilator aerosols.[3,8,47–51] It is especially helpful in respiratory acidosis.

It is generally assumed that during inspiration, positive pressure by mask is comparable to the negative pressure by body respirator and that during expiration, negative pressure by mask is comparable to positive pressure by body respirator.[44,51,52] This is probably true for normal lungs. However in patients with changes of viscoelastic properties of the lungs, these pressures might not be transmitted as exact equivalents since the equilibrium of the elastic and coordinating structures has been upset by the uneven damaging of the intermediate tissues.

We would stress again that this form of pressure breathing should not be employed in patients under circulatory stress, e.g., patients who are on the verge of or in peripheral vascular collapse, heart failure or those having spinal anesthesia.

The application of positive pressure during inspiration and negative pressure during expiration has recently been the subject of extensive study by Barach and Maloney and their associates, and other groups.[22,23,31,32,42–44,51–56] Barach and his associates have described their technic as exsufflation with negative pressure (EWNP) and have demonstrated its usefulness in the removal of pulmonary secretions in a variety of pulmonary and non-pulmonary disorders.[22,53–56] Maloney et al. have stressed the importance of the negative pressure phase in mechanical respirators, demonstrating the greater safety of employing alternating positive and negative pressures (P and N pressures).[42–44,51]

Numerous devices have been employed for the production of exsufflation with negative pressure, particularly the Coflator—O.E.M. unit[22] and the Exsufflator—Eliot unit.[23] There are also numerous P and N pressure devices commonly employed for resuscitation purposes. We are presently studying the application of positive and negative pressure breathing in the treatment of various pulmonary disorders complicated by retention of bronchial secretions. Barach and his associates demonstrated the clinical value of gradual inflation of the lungs followed by a high volume flow rate during expiration, produced by a sudden, rapidly induced negative pressure during expiration. This technic facilitated the removal of mucoid and purulent sputum from the lungs in a large number of their patients. The expiratory flow rate exceeded that produced during cough by many of their normal subjects and their patients with bronchial asthma, chronic pulmonary emphysema, bronchiectasis or poliomyelitis. This type of therapy has found its greatest usefulness in patients with inadequate cough mechanisms.

We are presently employing in our studies the Vent EL Aire, a multipurpose air pressure breathing unit that combines the four therapeutic functions of: (1) IPPB/I—intermittent positive pressure breathing during inspiration; (2) E.W.N.P.—exsufflation with a rapid negative pressure (cough); (3) resuscitation—by means of alternating positive pressure on inspiration with passive or negative pressure on expiration; (4) therapeutic aerosols—independent supply of therapeutic aerosols during inspiration only.

This apparatus may be used in a variety of pulmonary disorders depending upon which function is employed. (1) IPPB/I with bronchodilator aerosols: for the management of progressive bronchospastic disorders, such as chronic bronchial asthma and pulmonary emphysema; (2) E.W.N.P.: as a cough machine for the removal of bronchopulmonary secretions in the treatment of atelectasis, bronchiectasis, lung abscess, postoperative pulmonary aspirations, poliomyelitis, etc.; (3) resuscitation: whenever indicated; and (4) for the independent administration of therapeutic aerosols employing bronchodilator, antimicrobial, enzymatic or detergent agents.

The basic functions of the Vent EL Aire are carried out as follows:

1. When the dial is adjusted for IPPB/I the machine becomes a complete demand unit with positive pressure on inspiration only and passive expiration. The time of inspiration

(approximately one to three seconds) and the desired positive pressure (0 to 40 cm. H_2O) are both adjustable. Upon reaching the preset positive pressure the machine shuts off the air flow and allows the patient to breathe out passively. A slight inspiration by the patient starts the positive pressure and the cycle is repeated. Therapeutic aerosols (e.g., bronchodilators) are provided during inspiration only with the use of the enclosed auxiliary air pump unit.

2. When the dial is adjusted for "cough," the apparatus supplies controlled demand positive pressure on inspiration with adjustable pressures ranging from 0 to 40 cm. H_2O. The time during which the patient becomes inflated (approximately one to three seconds) is adjustable by means of an air flow control. Upon reaching the preset positive pressure, the machine automatically cycles to negative pressure. This shiftover occurs in .04 seconds by means of an electrical solenoid valve. The negative pressure is adjustable for 0 to 40 cm. H_2O. By dropping the mask or mouthpiece of $+40$ cm. during inspiration to -40 cm. H_2O during expiration, a rapid expiratory air flow rate is produced, simulating the human cough. The time for the negative or expiratory phase is controlled by an electric time delay mechanism which is adjustable from one to three seconds. The pressure changes are visible at all times on the face dial gauge.

3. Resuscitation may be accomplished by setting the desired positive pressure and a small amount of negative pressure on expiration (P and N pressures). The automatic time delay mechanism on expiration is put into operation with patients with no demonstrable or very shallow respirations. When the patients starts to breathe again the unit may be turned to demand intermittent positive pressure breathing—inspiratory only. This function should be set up with an anesthetic tracheal airway and mask in place.

4. The Vent EL Aire unit also contains an auxiliary oil-free diaphragm air pump with tubal connection to a nebulizer inserted into the mouth or face piece. This function provides the necessary air flows for the production of therapeutic aerosols during inspiration only. In this manner bronchodilator (e.g., vaporefrin), antimicrobial (e.g., penicillin), enzymatic (e.g., pancreatic dornase), or detergent (e.g., alevaire) aerosols may be administered whenever indicated.

SUMMARY

1. Advances in the use of therapeutic aerosols, oxygen therapy and pressure breathing therapy in the management of patients with chronic bronchial asthma, pulmonary emphysema and suppurative lung disease are discussed.

2. A new air pump apparatus for the production of all types of continuous aerosol therapy and the Neb*EL*izer croup tent apparatus for the administration of cold water vapors (humidity therapy) and alevaire (detergent agent) therapy are described.

3. The use of three new therapeutic aerosols —an anticholinergic agent (pamine bromide) of value in certain types of bronchoconstriction, pancreatic dornase, a pus-liquefying enzyme of value in evacuating bronchial secretions, and dusts and emulsions of cortisone and hydrocortone for allergic nasal states—are discussed.

4. The hazards of the carbon dioxide intoxication syndrome and respiratory acidosis in patients with chronic anoxia secondary to chronic pulmonary emphysema and pulmonocardiac disease are presented. Their recognition, prevention and specific management are briefly discussed. The hazard of opiate-induced respiratory acidosis is considerably reduced with the availability of nalline, a remarkable opiate antagonist.

5. The physiologic changes associated with pressure breathing therapy and clinical applications are discussed. Typical recordings of the physiologic effects of IPPB/inspiratory and alternating positive-negative pressures are discussed.

6. A new multipurpose air pressure unit, the Vent EL Aire, combining four of the main therapeutic functions in inhalational therapy is described for the first time.

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Surgical Implications of Solitary Tumors of the Lung

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SOLITARY tumors of the lung represent a deceptive clinicopathologic paradox, for behind their innocuous radiographic appearance lurks a high malignant propensity. By definition these lesions possess all the earmarks of a benign process. To the casual observer neither the size nor shape is a source of much concern. To the smooth border and peripheral location of these lesions add a general lack of symptoms and the deception is complete. The disguise is apt to be fleeting, however, for if one chooses to observe these patients, a regrettably high proportion will ultimately develop symptoms and die from local invasion and metastasis. The purpose of this paper is to reemphasize the hazards inherent in this group of tumors and to renew our earlier plea for their prompt excision.

Besides being one of the first to cite this danger[1] the senior author has reported what is acknowledged to be the highest cancer rate yet quoted for these lesions.[2] Since this figure has been widely referred to in the literature and its accuracy occasionally questioned, the thought occurred that an analysis of a comparable series of patients subsequently operated upon might prove interesting and informative. Accordingly, this report comprises a comparative study between the original sixty-seven patients reported in 1950 and the next sixty-seven consecutive patients operated upon for a solitary tumor of the lung. As will be shown, the two groups are remarkably similar.

Patients have been selected on the basis of the same radiographic criteria which we previously proposed in 1947.[1] (1) The tumor must be located within lung substance and aerated lung tissue must be visualized on all sides; (2) it may be round, ovoid or slightly lobulated in shape; (3) its edges are circumscribed and its contour is smooth; (4) there is no calcification within the tumor and (5) there is no evidence of cavitation. Excluded from this series are all tumors with associated pneumonitis, atelectasis or regional lymphadenopathy. Hilar, mediastinal, diaphragmatic and chest wall masses are ruled out by the presence of aerated lung around the tumor. In other words the tumor must be situated in the peripheral portion of the lung. Extreme sharpness of outline has not been required. Cavitary lesions are not included, because the many terms applied to solitary tumors (viz., solitary nodule, coin lesion, etc.) all imply that the mass is solid. This is just as well, inasmuch as cavitation is in itself generally accepted as an indication for resection, whereas the solid nodule is not. No lesion is included in which calcification can be demonstrated, for it is believed that their inclusion would weight the statistics in favor of the benign lesion. This is certainly true of nodules which are completely calcified, those stippled with calcium or those presenting a concentric ring type of calcification. It is only a little less emphatically true of practically all partially calcified nodules, although rare exceptions are noted.[3] Restrictions as to size of the nodule have been proposed by some authors,[4,5] but to us this seems relatively unimportant when considering the possibility of bronchogenic carcinoma, since size alone is no guarantee against malignancy. True, the small nodule is less likely to be carcinoma than the large nodule, but the large lesion was once small and it was then that treatment should ideally have been applied. Finally, unlike several other series, we have not required that the patient be asymptomatic. By far the majority of these patients are asymptomatic, yet a surprising number develop vague com-

plaints after learning of the presence of intrapulmonary pathology. Since moderately severe symptoms favor malignancy, we should state that none of the patients in this series had more than mild complaints.

TABLE I
ORIGINAL SIXTY-SEVEN CONSECUTIVE SOLITARY INTRAPULMONARY TUMORS

Condition	Number
Malignant*	
Bronchogenic carcinoma	32
Metastatic malignant tumor (kidney, 1; testis, 1)	2
Bronchial adenoma†	1
Lymphoblastoma	1
Neurogenic sarcoma	1
Non-malignant‡	
Granuloma	18
Chronic pneumonitis	4
Hamartoma	2
Cyst	2
Pleural mesothelioma	2
Lipoid granuloma	1
Myofibroma§	1

* Thirty-seven cases (55 per cent); thirty-three men and four women.

† Originally diagnosed as a bronchogenic carcinoma but reclassified after further study.

‡ Thirty cases (45 per cent); fourteen men and sixteen women.

§ Classified by some as a form of hamartoma.[15]

In comparing these two series of patients one is immediately struck by their similarity. Of the original sixty-seven solitary intrapulmonary tumors thirty-seven (55 per cent) were malignant (Table I); among the next sixty-seven, thirty-four (51 per cent) were malignant. (Table II.) Insofar as the malignant lesions are concerned the only real distinction between the two groups is a considerably higher incidence of metastatic carcinomas among the second series of patients. Although the relative number of men and women is not appreciably different in the two series, there is a surprising disproportion in sex distribution between the two groups with malignant tumors. Thus in the first group only 12 per cent of the malignant lesions occurred in females, whereas in the subsequent series 30 per cent were in women. Although we would be quick to admit that this difference is probably unique and not representative, it emphasizes nonetheless that the patient's sex has no real bearing on the possibility of any particular case being carcinoma. As for age the two groups are quite comparable, the first averaging 52.9 years and the second 49.4 years. Worth noting is that six of the original thirty-seven patients with malignant

TABLE II
NEXT SIXTY-SEVEN CONSECUTIVE SOLITARY INTRAPULMONARY TUMORS

Condition	Number
Malignant*	
Bronchogenic carcinoma	26
Metastatic malignant tumor (kidney, 2; bone, 1; breast, 1; ovary, 1; bowel, 1)	6
Bronchial adenoma	1
Hodgkin's disease	1
Non-malignant†	
Granuloma	27
Hamartoma	2
Cyst	1
Chronic pneumonitis	1
Pleural mesothelioma	1
Fibroma	1

* Thirty-four cases (51 per cent); twenty-five men and nine women.

† Thirty-three cases (49 per cent); seventeen men and sixteen women.

tumors and seven of the last thirty-four were less than forty-five years of age. In other words, about one of every five malignant tumors occurred in a patient who had not yet reached the so-called "cancer age." Moreover, just as youth provides no assurance against malignancy, it is no more logical to assume that the older patient necessarily has cancer, for in the second group there were six patients over sixty-five years of age, only two of whom had bronchogenic carcinoma, one having a bronchial adenoma and three, a granuloma.

Bronchogenic Carcinoma. Taken individually bronchogenic carcinoma constitutes the largest single contributor to this group of solitary lesions. This study confirms the commonly accepted precept that the cellular pattern of peripheral carcinomas shows a reversal of the usual distribution. Thus adenocarcinomas constitute over half of the carcinomas in this series, whereas when considering all bronchogenic carcinomas regardless of location only about 13 per cent prove to be adenocarcinomas.[6]

Metastatic Carcinoma and Sarcoma. Twice in the first series and six times in the second we

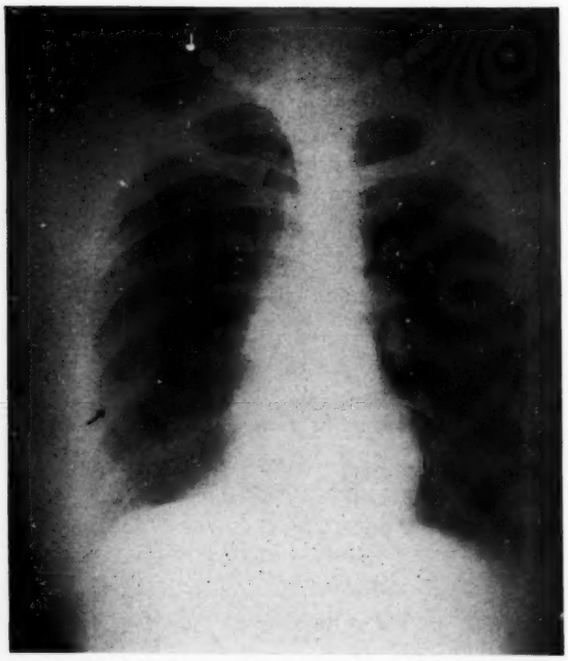


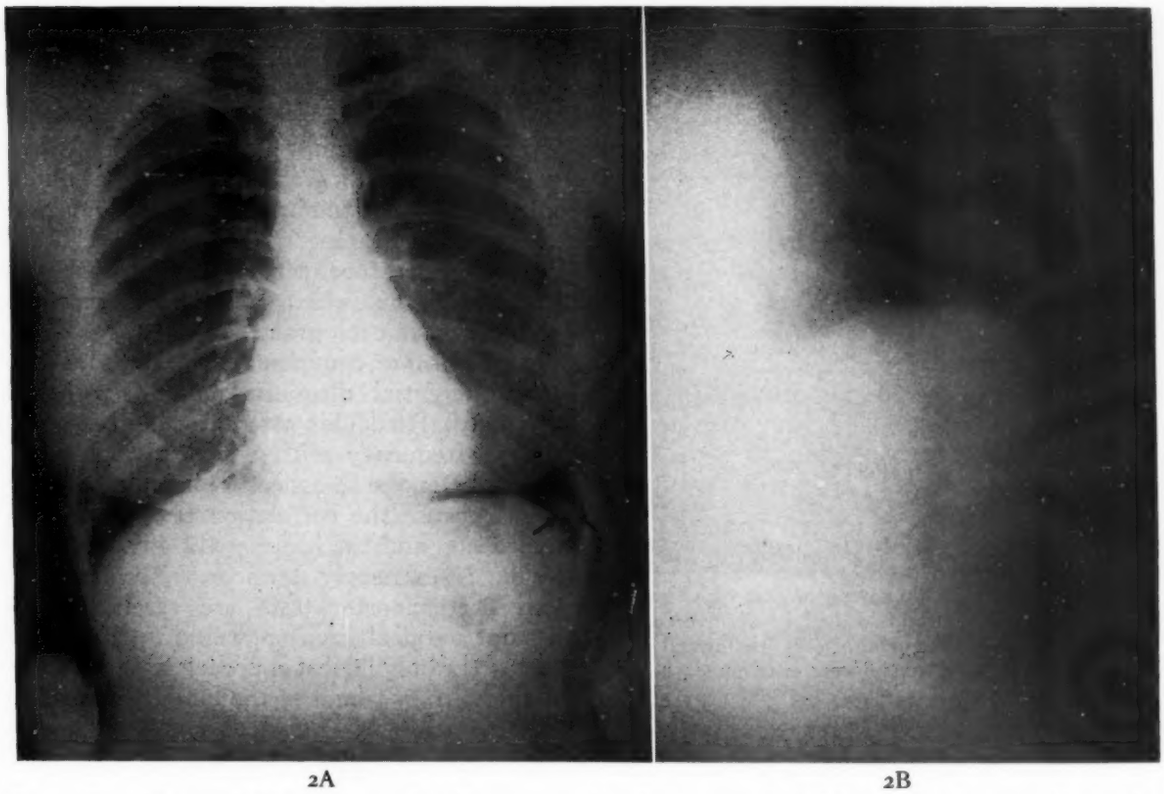
FIG. 1. Fifty-four year old asymptomatic white woman who had never smoked. A left radical mastectomy had been performed two months previously for adenocarcinoma of the breast. Intrapulmonary nodule in right lower lobe was resected and proved to be primary epidermoid bronchogenic carcinoma.

resected solitary metastatic nodules. Frequently there is no suggestion preoperatively that the lesion is metastatic. Even when there is, it is extremely difficult, expensive and time-consuming to find the primary without some clue to its origin. For this reason we prefer to remove these nodules after a reasonable but not overly elaborate study. If it proves to be metastatic, then the histology generally suggests the site of the primary.

When a primary extrapulmonary tumor has previously been excised, the chief determining factors in the chance for cure would appear to be the type of tumor with which one is dealing and the time interval between previous surgery and the appearance of the solitary metastasis in the lung. Even so, it should be emphasized that once a secondary tumor appears in the lung, widespread metastases generally show up rather promptly. In one careful study it was concluded that with several exceptions the patients with a long hiatus between the removal of the primary and secondary tumors did no better than the group as a whole.[7] This is exemplified by one patient in our second series who, after removal of a clear-cell carcinoma of the right kidney, survived twelve years before a metastatic nodule appeared in the left lung, only to have signs of cerebral metastasis develop within a month after excision of the pulmonary metastasis. Perhaps the most important aspect to this problem is this: the presence of a solitary intrapulmonary nodule in a patient wth a primary malignant tumor elsewhere is no proof that the pulmonary nodule represents a metastasis. Actually it may be a primary bronchogenic carcinoma as was true of a fifty-four year old woman in our second series who had recently undergone left radical mastectomy for adenocarcinoma. The small nodule noted in the right lung (Fig. 1) was presumed to be a solitary metastasis, but following resection it was found to be a primary epidermoid carcinoma. As a result of our experience with this and several similar cases we have become extremely reluctant to consider a history of previous cancer surgery as a reliable guide to the identity of a solitary intrapulmonary tumor.

Bronchial Adenoma. Even when unaccompanied by frank evidence of malignancy bronchial adenomas remain potentially malignant tumors and have been so classified in this study. As a rule they are centrally located, hence, as one might imagine, they should seldom enter into the differential diagnosis of solitary tumors of the lung. While this has proved true in our experience, it should be pointed out that in at least one series of solitary circumscribed lesions bronchial adenomas represented a substantial portion of the total number, namely, 7.7 per cent.[8] In our combined series we have encountered only two such cases, both occurring in the middle lobe.

Granuloma. The most common benign type of nodule occurring in the lung is the granuloma. Eighteen such lesions were included in our original series, while twenty-seven have been encountered in the second. Thus of all the solitary tumors included in this study 36 per cent were granulomas. As implied by the nonspecificity of the term "granuloma" the exact identity of all of these lesions has not yet been ascertained. The traditional view is that these are tuberculomas, but the tubercle bacillus appears to have been accused unfairly. This is not to say that none are true tuberculomas. Assuredly, when acid-fast bacilli are demonstrated by smear, culture or specially stained tissue sections, the lesion is indeed a tubercu-



2A 2B

FIG. 2. Forty-five year old asymptomatic white woman. A, solitary tumor in left lower lobe discovered in routine chest roentgenogram. B, no calcium visible in planigram. Lesion resected and found to be packed with histoplasma. Diagnosis: histoplasmoma.

loma. More often than not, however, these lesions prove to be bacteriologically negative, and the diagnosis is then seriously in doubt. From a rather broad personal experience with the periodic acid-Schiff (PAS) stain[9,10] we are convinced that many of these granulomas are in reality indolent mycotic foci. With few exceptions[8,11] the etiologic fungi, due apparently to the fact that they are either dead or dying, can seldom be recovered by cultures[12] and are generally invisible in ordinary hematoxylin and eosin stained tissue sections. Utilizing the PAS stain, histoplasma or less commonly some other pathogenic fungus can be demonstrated in a fair number of these granulomas. From our studies to date as well as those of others[12–14] we suspect that the histoplasmoma is more common than the tuberculoma. In view of our failure to isolate the responsible fungi by culture, we presume these foci to be healed or healing and for that reason we are reasonably certain that they do not on their own merits deserve resection. Unless calcification is demonstrable radiographically, however, we do not believe that they can be reliably differentiated from a small, circumscribed carcinoma by any means short of resection. (Fig. 2.)

Chronic Pneumonitis. Chronic pneumonitis without any apparent granulomatous component will occasionally take the form of a solitary intrapulmonary nodule. Only one such diagnosis was included in the second series of cases suggesting that closer scrutiny will relegate most of these lesions to the category of granulomas.

Hamartoma. Hamartomas have always been considered extremely rare benign tumors of the lung, when in effect they are probably not too uncommon. This would seem to be substantiated by the fact that in one series hamartomas comprised 16 per cent of all solitary lesions.[8] In our combined series we have seen only four hamartomas and two of these were removed from the same patient, the second appearing five years after excision of the first. If it were possible to make a preoperative diagnosis of hamartoma, we believe that surgery would be unnecessary, since these tumors are benign and do not as a rule attain very

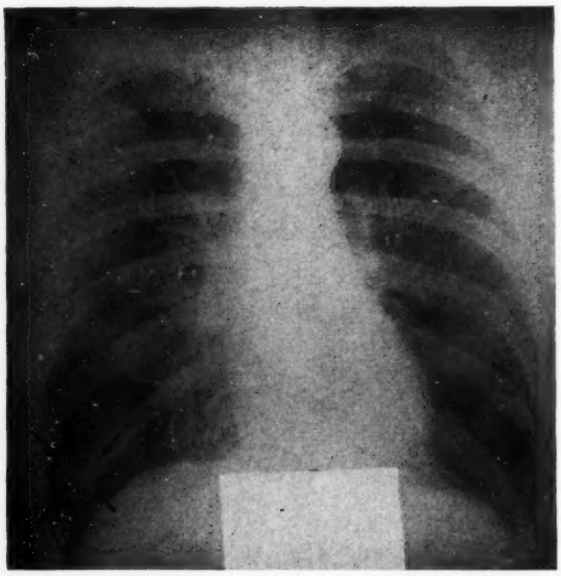


FIG. 3. Sixty-two year old asymptomatic white man. Solitary tumor of the right lower lobe discovered in routine chest x-ray. Pneumonectomy performed for primary epidermoid bronchogenic carcinoma. Note similarity to Figure 2.

large proportions. In this regard the tendency of hamartomas to calcify actually strengthens our belief that calcific nodules do not warrant surgical excision unless enlarging. In the absence of calcium, however, it is impossible to differentiate a hamartoma from a carcinoma and resection is necessary to establish the diagnosis.

Pleural Mesotbelioma. Pleural mesotheliomas are definitely unusual tumors. The localized fibrous type of pleural mesothelioma commonly presents the radiographic appearance of a solitary tumor of the lung although in effect they are not truly intrapulmonary. Clubbing of the digits and arthritis, which are frequent accompaniments of this tumor, were noted in none of the three patients in this series with pleural mesotheliomas. Even when present such signs help in no way to exclude bronchogenic carcinoma. Moreover, the tremendous size that these tumors eventually reach, is reason enough to justify their excision. Histologically it is extremely important to differentiate pleural mesotheliomas from fibromas, fibrosarcomas, neurofibromas and neurofibrosarcomas which are the usual but erroneous pathologic interpretations of these tumors.

Other diagnostic possibilities among the solitary intrapulmonary tumors include chronic abscess, pulmonary cyst, hemangioma, lipoid granuloma, fibroma, fibrosarcoma and other comparably uncommon entities.

SUMMARY

1. Two large groups of patients, all of whom presented the radiographic picture of a solitary intrapulmonary tumor, have been analyzed and compared.

2. The incidence of malignancy, as we have previously emphasized, is extreme, being over 50 per cent in each group.

3. The more common lesions entering into the differential diagnosis have been briefly discussed. Particular attention has been paid to the frequency with which histoplasmosis accounts for the so-called "tuberculoma."

4. Because the correlation between clinical impression and the histology of any particular lesion is extremely tenuous, and since the various diagnostic tests are rarely helpful, prompt surgical excision would seem to constitute the only logical approach to the problem of the solitary tumor of the lung.

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Pulmonary "Coin" Lesions

MEDICAL AND PATHOLOGIC ASPECTS

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A RECENT definition of "coin lesions" proposed by Storey et al.[33] gives the following limiting criteria: (1) 1.0 to 5.0 cm. in size; (2) round or oval in shape, with sharply circumscribed borders; (3) surrounded on all sides by normal-appearing lung; (4) no symptoms; (5) homogeneous in density or containing calcium; and (6) solitary. This would eliminate large masses with adjacent inflammatory reaction associated with atelectasis or those obviously arising in the chest wall or mediastinum. It would also eliminate a typical Ghon complex.

These lesions are listed in the literature under various names, such as solitary intrapulmonary tumors (Davis and Klepser;[10] Effler, Blades and Marks[13]), isolated pulmonary nodules (Sharp and Kinsella[31]), single circumscribed intrathoracic densities (Abeles and Ehrlich[1]), silent lung disease (Overholt[29]), isolated intrathoracic nodules (Wolpaw[36]), solitary round lesions (Eighth Pembine Conference[30]), or solitary circumscribed lesions (Hodgson and McDonald[22]).

The term "coin lesion" is adequately descriptive from its x-ray appearance and is well understood by the profession. It is not an ideal term but has achieved acceptance by common usage.

Considerable literature has accumulated on this subject since Graham, in 1933,[17] showed that pneumonectomy was a feasible procedure and, in 1936,[18] reported on resection of calcified pulmonary abscess in three cases, all of which proved to be tuberculomas. Alexander[4] called attention to such lesions in 1942 and, characteristically, covered the problem at that early date well and completely. He pointed out that these approximately similar x-ray shadows may represent diverse types of benign and malignant lesions and that any diagnosis from clinical study alone is of interest but of little importance. What is of paramount importance is whether a nodule is benign or malignant and, if malignant, whether it is still completely removable. Preoperative determination can be made only rarely. Therefore, all patients with presumably removable nodules should be operated upon. The literature to date provides ample confirmation of his point of view at that time.

When an abnormal shadow of this description appears on the chest roentgenogram, there is a lamentable tendency in some quarters to "watch it." I believe that very few experienced chest physicians will agree with this practice. There is a large gamut of tests now available: examination of the cells and bacteriologic study of the sputum, if any, and, if no sputum, tracheal wash or gastric lavage; bronchoscopy, with bronchial aspiration and biopsy; blood counts and chemistry; serologic studies; various intradermal tests, usually for tuberculosis, coccidioidomycosis, histoplasmosis and echinococcus; various x-ray procedures, including stereoscopic and body section radiography; biopsy of retrosternal and deep supraclavicular nodes, etc. However, when all of these studies have been accomplished, including whenever it is thought that such a lesion may be metastatic, gastrointestinal x-ray series, urologic studies with pyelograms, gastroscopies, proctoscopies, x-ray study of the bones, etc., one still sees the shadow on the x-ray film without having achieved a positive and confirmed diagnosis.

The problem with a "coin" lesion is not so much an exact clinical diagnosis as an immediate and pressing question of whether or not this x-ray shadow represents carcinoma. This question can usually be answered definitely only by exploratory thoracotomy. If the shadow represents carcinoma, no time can be lost in removing it—no time can be lost in establishing the exact diagnosis and following through with the necessary surgery which, with most men, would be total pneumonectomy if the condition of the patient permits. Many of these lesions will be benign tuberculomas and other granu-

lomas, in which case a few days' or weeks' delay would be of less importance. However, there must be a very brief portion of time when a carcinomatous lesion can be entirely resected. There is another instant after which any surgical procedure now known would be too late because the original lesion would have already metastasized. Time then is of the essence. It would, therefore, not seem wise to embark on time-consuming differential diagnostic procedures, most of which are likely to be negative, as emphasized by Wolpaw.[36]

Carcinoma of the lung is obviously increasing (Boyce[7]). Adler,[3] in 1912, could collect only 374 cases of carcinoma of the lung from the world literature. In 1950, there were 21,219 deaths recorded from carcinoma of the lung in the United States alone.[32] Surgery is the only means we have at this time to cure carcinoma of the lung completely. Surgical results, at best, are not as favorable as we would like. Too many patients come to the surgeon in advanced stages and are already inoperable when first seen. As pointed out by Boyce,[7] it is disastrous to assume that because pneumonectomy is not accomplishing very much it is a dangerous and useless operation. It is no longer dangerous and the reason it is accomplishing so little is that there are so few opportunities to demonstrate its possibilities. How, then, can we afford not to make a positive diagnosis of the lesions visible by x-ray in order to rule out carcinoma as the cause of the abnormal shadow?

REVIEW OF THE LITERATURE

Abeles and Ehrlich,[1] in a study of forty-four patients carefully worked up, showed that few diagnoses were definitely established before exploratory thoracotomy. In twenty-one patients operated upon, seven had primary pulmonary malignancies. Ten refused surgery, six of them on the advice of their family physicians; in five of the ten definite malignancy subsequently developed.

Davis and Klepser[10] had a similar experience in some sixty-seven cases in which thirty-seven (55 per cent) were malignant. In forty cases referred in private practice, twenty-eight (70 per cent) were malignant, the average age being 52.9 years. In the sixty-seven cases, forty-seven were males and twenty females, the ages varying from twenty-five to seventy-four years.

Sharp and Kinsella,[31] in discussing the significance of the isolated pulmonary nodule, reported ninety-six cases over a four-year period. Their patients ranged in age from twelve to eighty-five years. Growth of a nodule is not necessarily a sign of cancer for it was noted in fibroma, hamartoma, adenoma and granuloma, while lack of growth for many months may be observed in carcinoma. In forty-one of their ninety-six cases, surgical exploration was refused and a confirmed diagnosis was not available. In the other fifty-five patients the diagnosis was proved: fifteen (27 per cent) of these were malignant; twenty-two (40 per cent) inflammatory; and eighteen (33 per cent) were benign tumors. The authors concluded that the only reliable and accurate diagnostic procedure is exploratory thoracotomy, with excision and prompt pathologic examination of the mass. Even with the lung exposed in the surgeon's hand, it is often impossible to state accurately the nature of the nodule, and they believe that, in general, indirect studies cannot be expected to furnish the answer. At the beginning of their study Sharp and Kinsella made exhaustive clinical studies in attempting to reach a correct clinical diagnosis but concluded that these studies were not worth while.

An editorial[12] poses the question, "Shall these lesions be observed or operated upon for diagnosis and therapeutic considerations?" It points out that there is a low operative mortality and that there is no other way to achieve a positive diagnosis. In the various series of such patients reviewed and reported, 15 to 30 per cent of the lesions were malignant.

Effler, Blades and Marks,[13] in a study of twenty-four young service personnel, found that even in this young group 15 per cent of the lesions were malignant, with no mortality from surgery itself.

Grow, Bradford and Mahon,[19] reporting on 200 young service men hospitalized at Fitzsimons United States Army General Hospital, found 25.6 per cent of such pulmonary lesions malignant.

Mahon and Forsee,[25] in a study of fifty-five lesions thought to be tuberculomas, reported seven tumors; four (7 per cent) were malignant. Thirteen other lesions were described and the authors stated that, in spite of employing every possible diagnostic procedure to arrive at a correct diagnosis, each of these lesions

was suspected at some time of being a tuberculoma and only on pathologic examination after removal was the correct diagnosis established. They advise wedge resection to establish diagnosis. They had no operative deaths. It is their belief that in such cases the operative risk is no greater than in appendectomy. Their patients ranged from nineteen to fifty-four years, the average age being thirty-two years.

Bugden[8] aptly compares the operative procedure in "coin" lesions with that in the study of breast lesions in which biopsy is readily accepted.

O'Brien, Tuttle and Ferkaney[27] believe that these lesions will usually fall into one of four groups: (1) malignant or benign tumors; (2) tuberculomas; (3) chronic indolent abscesses; or (4) metastatic tumors. In reporting on twenty-one patients over two and a half years of age, in almost 50 per cent of the patients operated upon the lesion was a tumor and 90 per cent of these tumors were malignant. They point out that a malignant tumor will usually grow but that one cannot wait for this growth for diagnosis, as a small malignant tumor of the lung without growing *in situ* may metastasize extensively. They further point out that the age of the patient in whom the lesion appears is not always helpful in diagnosis. It is sometimes stated that under the age of forty, because most of these lesions are either benign or tuberculomas, operation is not necessary, but two patients in their series with carcinoma were under thirty-five years of age and two of the eight patients in their series with tuberculomas were over fifty.

Overholt and Schmidt,[28] discussing in 1949 the silent phase of cancer of the lung, stated that the problem was magnified by an astounding recent increase in numbers, yet simplified by facilities for early detection. They showed that excision was feasible, relatively safe and effective, and emphasized that physicians now have the tools to find, label and successfully treat cancer of the lung. In 1951, Overholt[29] pointed out that different pathologic processes in the lungs may produce identical shadows on x-ray films, while conversely the same disease may produce different shadows. In his series it was impossible to establish an absolute diagnosis preoperatively in more than two-thirds of the patients in whom excisional therapy was indicated. He stated that in 61 per cent of the cancers seen during the past year diagnosis could not be established until after exploration. In 162 cases explored, fifty-eight lesions were tumors of which 67 per cent were malignant.

At the Eighth Pembine Therapy Conference held in September, 1951, there was considerable discussion on resection of solitary round lesions.[30] There was almost unanimity of opinion that such lesions should be resected. Attention was called to the fact that the presence of calcification in these lesions does not necessarily rule out the possibility of malignancy.

Harrington,[20] in his series of 291 various types of extrapulmonary and intrapulmonary lesions, reported fifty-two patients with no symptoms. In this group of fifty-two cases, twelve lesions were found to be malignant, nine being early primary processes, and surgical removal was achieved at a time when results are most favorable.

Boyce,[6] in 1953, stated that only when pneumonectomy can be carried out promptly in respect to the pathologic process, not the symptoms, are the results of treatment rewarding. In this study of the causes of death in patients with carcinoma of the lung in a large public hospital, he concludes that, if this group of fatalities teaches us anything at all, it is that suspicious lesions in the chest must be explored on suspicion alone, without delay for time-consuming positive diagnosis. If the lesion is found to be a tuberculoma, a lung abscess or a benign lesion, surgery is still the procedure of choice.

Liebow[24] in discussing tumors of the lower respiratory tract states that since it is necessary to establish an accurate diagnosis when any intrathoracic tumor presents itself, exploration is indicated in view of the small risk of thoracotomy and the danger of allowing a malignant intrathoracic tumor to remain untreated.

DeBakey,[11] in his discussion of the problem of carcinoma of the lung, states that the demonstration of an abnormal x-ray shadow demands aggressive action to establish the diagnosis. When other measures fail to reveal the exact nature of the lesion, prompt exploration is indicated. The risk of exploration, except in the aged and debilitated, may now be considered less than that involved by the consequences of delay. He points out that this is an urgent public health problem and advises routine x-ray of the chest every six months in

men over forty, to help control the rising death rate from cancer of the lung.

In 1953 Storey, Grant and Rothmann[33] reported on forty patients with coin lesions of the lung, ages nineteen to seventy. Most of these were young men in the service. All of the lesions were detected by routine x-ray; 17.5 per cent were found to be malignant. They state that surgical excision without undue delay is the treatment of choice.

Hood et al.[23] emphasized that complacency is no longer justifiable on the part of an attending physician who discovers a solitary circumscribed lesion of the lung with its recognized malignant potentiality. Generally there are no symptoms, so patients are not impressed. The peripheral location of the lesion makes important diagnostic aids available for the study of most diseases of the chest ineffective. In their study of 156 cases in which resection was performed, 35 per cent of the lesions were malignant. Evidence of growth increased the suspicion of malignancy; size alone was not a help. They advised that preoperative diagnostic study in those patients in whom calcium is not demonstrable should be: (1) adequate examination of sputum for malignant cells, (2) a blood sedimentation rate and (3) a tuberculin test. Prolonging the diagnostic study beyond this is in most cases without justification, and the decision regarding operation should not be delayed on this account. Their attitude toward calcium will be discussed later.

My own attitude toward examination of sputum or tracheal or bronchial washings for malignant cells in the diagnosis of these lesions has crystallized in recent months. This procedure is an interesting technical study but of little real practical importance. If a positive diagnosis is made through examination of the cells in the sputum, the lesion must be resected if possible. If this examination is negative and carcinoma is not completely ruled out, exploratory thoracotomy is still definitely indicated. A prolonged search of sputum specimens in attempting to achieve an exact pathologic diagnosis would then seem to be a waste of valuable time and delays the necessary surgery.

Vivas and Crabtree,[35] Brooke Army Hospital, bring up an interesting point. They state that all lesions of medium and small size of light density should be considered malignant, that lesions of medium and small size of medium density should be studied carefully, and that lesions of heavy density are less likely to be malignant. They stress the value of previous chest films. They believe that all lesions over 3 cm. should be considered malignant. Their conclusions are based on a study of fifty cases. This matter of density would seem to be a difficult point to decide because of differences in x-ray technic, even under controlled conditions.

May, Rose and Dugan[26] reported in 1954 that in 40,000 routine admission chest x-rays taken in a Veterans Administration Hospital sixty unsuspected solitary lung lesions were found. Twenty-four of these were diagnosed and treated by surgical removal, and twelve were diagnosed by other methods. Of these thirty-six, eight (22 per cent) were primary bronchogenic carcinomas. They recommend that "coin" lesions be excised for diagnosis because usually the nature of such lesions cannot be detected save by surgical resection and microscopic study. Like DeBakey,[11] these authors also believe that routine roentgenographic examination of the chest at six-month intervals is advisable, especially for men over forty years of age, since asymptomatic tumors routinely detected are often confined to the lungs.

Whether or not the lesion containing calcium should be resected promptly has caused much discussion.

In a study of calcification, using tuberculous lesions both for clinical and experimental study, Bloch[5] showed that the degree of calcification on the x-ray is arbitrary and is largely dependent on special x-ray technics for its demonstration.

The Mayo Clinic Group in a series of papers[15,16,22,23] say that in a group of 156 cases in which resection was performed calcium was detected by body section radiography in 32 per cent of the granulomas, in 28 per cent of the hamartomas, but in no other lesion. They believe that the calcium reliably indicates benignancy. Good, Clagett and Weed[15] state that if the coin lesion contains calcium, watchful waiting is justified. Hodgson and McDonald[22] oppose the routine resection of coin lesions. They discuss calcium again, and warn that one must be sure that what is seen on the x-ray is truly calcium and that it does lie within the mass. It may occur in a number of pulmonary conditions, which they list. They say that the presence of true calcium within

the mass indicates that the lesion is not a carcinoma, except in the rare condition of a malignancy developing around a lung stone or a teratoma. Then, they state that some calcific lesions should be removed anyhow, depending upon the nature of the lesion itself.

Abeles and Chaves,[2] from the study of some thirteen cases, consider the presence of calcium strong evidence against malignancy. They state that such lesions should not be excised as exceptions to this are too few, and they advise tomographic films. Fink[14] and Culver et al.[9] also think that if a coin lesion contains calcium watchful waiting is justified.

On the other hand, Storey, Grant and Rothmann[33] state that the degree of assurance afforded by the presence of calcium within the mass is debatable. The amount of security offered by calcification within the coin lesion is relative rather than absolute and is not sufficient reason to withhold from the patient the potential benefits that may be derived from the histologic examination of the lesion after removal.

Tuttle[34] also states that the presence of calcium in a lesion does not assure that it is not carcinoma. Sharp and Kinsella[31] say that the old idea that all granulomas and calcifications in the lung are the result of tuberculosis has definitely been disproved. Calcium deposits do not establish the benign or malignant nature of the process.

May, Rose and Dugan[26] report a case of proved bronchogenic carcinoma which by x-ray appeared to contain calcium. Hodes[21] states that the presence of calcium in a pulmonary nodule does not exclude the possibility of a malignant pulmonary lesion. He has seen four patients with calcified nodules which ultimately proved to be bronchogenic carcinoma.

Finally, Good et al.[16] in a paper based upon the same 156 cases of the Mayo Clinic, stated that failure to show calcium does not mean that a lesion is malignant, but demonstration of calcium seems to be the only feature which is sufficiently accurate to allow us to postpone an operation indefinitely. The paper was discussed vigorously, and Dr. Good replied that tumors which do not show calcium should be excised as soon as found, while the calcified ones may be watched for a time, but that they too must be excised if they show evidence of growth or if the patient experiences hemoptysis, obstruction of a bronchus, or other symptoms of serious import. Dr. Hodes discussed these points as noted previously. Dr. Good closed by saying, "After all, I have never maintained that the calcified lesion should not be removed; I have said only that it could be watched longer."

Calcium, then, may be difficult to detect even when present. We see that the consensus is that in view of all the factors pro and con the apparent presence of calcium within the lesion should not bar its excision for the purpose of establishing a definitive pathologic diagnosis and ruling malignancy in or out.

The roentgenograms accompanying the following case reports are of patients on whom no definite diagnosis could be achieved from a battery of diagnostic tests. The x-rays actually have a similar appearance. There was no possibility of determining before exploratory thoracotomy which of these lesions were carcinoma and which were not. These x-rays are truly representative of average "coin" lesions.

CASE REPORTS

CASE 1. (Fig. 1.) C. F., a thirty-nine year old white woman, was first seen on November 2, 1951, complaining of a heavy tight feeling in the center of her chest with a dry cough and excessive perspiration on exertion. She had not felt well for the past year and a half.

Past history revealed a few chest colds and frank pneumonia in 1919 and 1944. She had had pleurisy in 1947. The only surgery was a kidney suspension in 1931. The family history was non-contributory.

Physical examination was normal, except for fluoroscopy of the chest which revealed a 2.5 cm. "coin" lesion close to the pericardium on the right but definitely within the parenchyma of the lung. Bronchoscopy, November 21, 1951, was negative except for flecks of mucoid sputum in the right lower lobe and slight redness of the orifice of the posteromedial section. Bronchial lavage at the time of bronchoscopy was negative for acid-fast bacilli and Papanicolaou stain showed: group III, doubtful; a few atypical epithelial cells seen in clumps; many erythrocytes.

Exploratory thoracotomy was performed on December 21, 1951, and the lesion removed.

Pathologic report revealed the following: the submitted specimen consisted of a portion of the lower lobe of the right lung weighing 40 gm. and measuring 10 by 5 by 5 cm. The

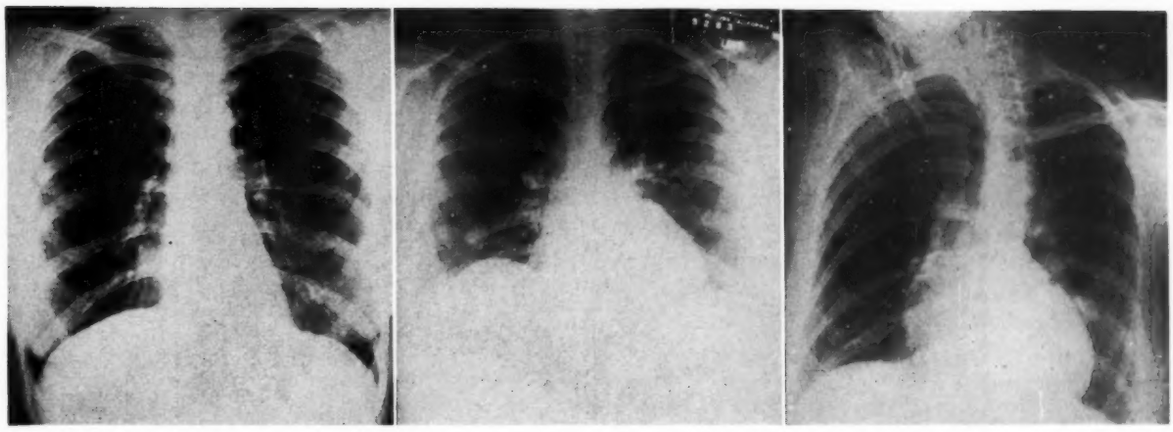

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FIG. 1. Case I. "Coin" lesion below hilus close to right cardiac border. Pathologic diagnosis: oat cell carcinoma.

FIG. 2. Case II. "Coin" lesion in right lower lung field. Pathologic diagnosis: fibrocaseous tuberculoma.

FIG. 3. Case III. "Coin" lesion in left lower lobe. Pathologic diagnosis: chronic non-specific inflammation.

pleura was smooth, moist and glistening and showed a mottled, pinkish and yellowish gray appearance. On section, the pulmonary parenchyma was congested and partially atelectatic and centrally, close to the bronchus, was a lobulated, nodular, fibrous lesion 3 by 2 by 2 cm. in size. The lymph nodes were pigmented. Submitted separately was a section of the inferior vein of the lower lobe; this was rather firm and indurated and measured 2 by 0.8 by 0.3 cm. Also submitted were the middle and remainder of the lower lobes of the right lung, weighing 250 gm. The bronchial tree was markedly dilated and contained mucous material. The pleura was smooth, moist and glistening. The pulmonary parenchyma was atelectatic and congested, being similar to that already described.

Microscopically the sections showed a growth composed of small basophilic oat cells with a characteristic basal appearance. These cells were infiltrating the mucous membrane of the bronchi and also the alveoli. Mitotic figures were numerous. Two of the six lymph nodes showed tumor. The tumor cells were similar to those seen in the primary growth.

Pathologic diagnosis was oat cell carcinoma.

Two and one-half years postoperatively the patient was doing well with no evidence of recurrence.

CASE II. (Fig. 2.) T. K., a twenty-seven year old white woman, was first seen on May 28, 1954, complaining of a persistent cough for two weeks and extreme fatigue for the past month. Her family physician had taken a chest x-ray which revealed a lesion in the lower portion of the right lung.

Past history was non-contributory. She had had a gallbladder operation in 1951, and had dieted from a maximum weight of 265 pounds down to her present weight of 235 pounds. The family history was also non-contributory.

Physical examination revealed a twenty-seven year old obese white woman, six months' pregnant. On x-ray there was an indeterminate lesion of the anterobasal segment of the right lower lobe, which had speckles of central calcification with a surrounding zone of solid nature. Clinical impression was "coin" lesion, right lower lung field.

Thoracotomy was performed on June 1, 1954, and the lesion removed.

Pathologic report was as follows: specimen labeled "right lung tuberculoma" was a globular firm mass that averaged 2.2 cm. in diameter. On section it consisted of concentric layers, all rather firm of fibrous consistency. The inner mass measured 1.0 cm. in diameter, was rather chalky gray-white, slightly friable. This was surrounded by a zone which was gray-tan in color and rather fibrous. Similar alternative fibrous capsules surrounded the entire mass. A small fragment of lung tissue was present. This measured up to 3.0 cm. Representative sections were taken for microscopic study.

Microscopically, sections of the specimen labeled "right lung tuberculoma" showed a nodule of eosinophilic necrotic tissue surrounded by a small zone of pulmonary tissue. The small amount of surrounding recognizable

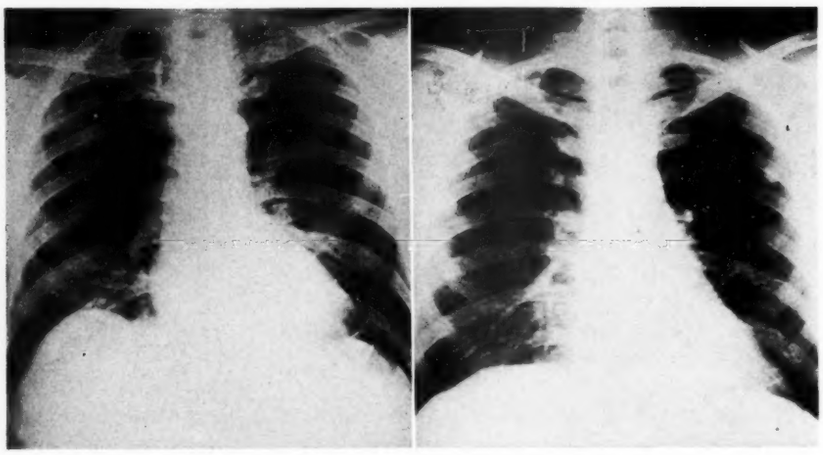

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FIG. 4. Case IV. "Coin" lesion in right upper lung field. Pathologic diagnosis: alveolar cell carcinoma.

FIG. 5. Case V. "Coin" lesion in left upper lung field. Pathologic diagnosis: fibrous and calcareous nodule, tuberculosis.

lung tissue showed considerable lymphocytic infiltration, diffuse fibrosis, slight anthracosis, and a thickening of the cells lining the alveoli. Sections stained by the Ziehl-Neelsen technic showed a small number of acid-fast bacilli within the necrotic nodule.

Pathologic diagnosis was fibrocaseous tuberculoma of lung.

CASE III. (Fig. 3.) V. C., a fifty-eight year old white woman, was referred to us on February 4, 1952, by her family physician who had been watching a rounded density at the left posterior heart base since August, 1951. This density had remained constant. Patient had been complaining of pain in her chest on exertion which radiated out to the arms.

Past history was non-contributory, except for the pain described. Electrocardiograms had been normal. Family history was also non-contributory.

Physical examination was negative, except for the "coin" lesion in the left lower lobe revealed by x-ray.

Exploratory thoracotomy was performed on February 9, 1952, and the lesion removed.

Pathologic report revealed the following: the submitted specimen consisted of a small mass of tissue from the lung measuring 3 by 1.5 by 1.0 cm. The pleura appeared smooth and glistening. On section a thin rim of lung parenchyma was present surrounding a central area which was cystic and contained greenish gray purulent material.

Microscopically, the sections showed an inflammatory lesion with no evidence of specific type granulation tissue. There were diffusely scattered round cells, plasma cells and histiocytes with some metaplasia of the bronchial epithelium. The alveoli were collapsed in many areas and in some places they showed hemorrhage and round cell infiltration. There was one area in which the alveoli showed an adenomatoid reaction with large, clear, granular cells. These were not sufficient, however, to cause any obstruction. They may represent a very minute, microscopic beginning adenoma. No evidence of actinomycosis, coccidioidomycosis or tuberculosis could be demonstrated.

Pathologic diagnosis was chronic non-specific inflammation.

When last seen two and a half years postoperatively the patient was doing well and her lungs remained clear.

CASE IV. (Fig. 4.) M. J. T., a fifty-nine year old white man, was first seen on December 19, 1950, complaining of a heavy burning sensation around his sternum and of a recent change in voice. There was constant clearing of his throat and he was feeling tired. He had considered himself quite well until a respiratory infection three weeks before. He dated his hoarseness from that time.

Past history was essentially negative except that the patient had lived around Phoenix, Arizona for the past eighteen years. There had never been any erythema nodosum. In 1948 he had a chest x-ray in Nogales, Mexico

and was told that he had a spot on his lung but that it was not thought to be of any importance. Family history was non-contributory.

Physical examination was negative except for some question of small, very deep axillary nodes, and fluoroscopy and x-ray of the chest revealed a discrete but irregular roundish density at the top of the right lung. Intradermal tuberculin and coccidioidin tests were positive. Bronchoscopy on December 26, 1950, was negative except for a white patch seen on the right vocal cord. Bronchial lavage at the time of bronchoscopy was negative for tubercle bacilli, for fungi or coccidioides, and Papanicolaou stain was considered negative.

Exploratory thoracotomy and segmental resection of the lesion were recommended at the time of examination, but the patient did nothing about it until March, 1951, when he entered the Veterans Administration Hospital, Los Angeles, California. On March 14, 1951, right upper lobectomy was performed. The patient withstood the procedure well and his postoperative course was smooth.

Pathologic report revealed a relatively small, circumscribed carcinoma of rather regular cytology and apparently of terminal bronchiolar or alveolar origin; no tumor extension was observed in anthracotic hilar lymph nodes examined.

Pathologic diagnosis was alveolar cell carcinoma, right upper lobe.

On July 7, 1952, over a year postoperatively, the patient was examined by the Surgical Tumor Board, at which time he was asymptomatic. A chest x-ray at that time was normal except for the postoperative changes.

CASE V. (Fig. 5.) L. H., a thirty-three year old white man, was referred to us on September 22, 1953, by his family physician because of a "coin" lesion in the left upper apex. Patient had been feeling under par recently and had noted elevation of temperature in the evening.

Past history revealed that on March 30, 1953, patient had a right spontaneous pneumothorax and was treated in the hospital for eleven weeks. Chest x-ray of July 27, 1953, showed complete re-expansion of the right lung. At that time the shadow in the left upper apex was found. The only known exposure to tuberculosis had been twelve years previously when the patient worked on a tuberculosis ward. The family history was non-contributory.

Physical examination was essentially negative, except for a positive intracutaneous tuberculin test. Culture of tracheal wash was reported negative six weeks later. Serial x-ray films showed the "coin" lesion to be constant.

Exploratory thoracotomy, with wedge resection of the lesion, was performed on January 15, 1954.

Pathologic report revealed the following: the specimen labeled "nodule from left upper lung" consisted of a rounded rather firm mass, measuring 1.2 cm. in diameter. A small amount of fibrotic lung tissue was on the outside. A concentrically arranged dense fibrous capsule measuring 2 mm. formed the second layer, and the center of the lesion was filled with grayish caseous material. There was a small amount of anthracotic pigment in the periphery of the specimen.

Microscopically, sections of the mass from the left upper lobe of the lung showed a mass with a fibrous capsule and a central degenerated fibrous substance with marked calcium deposit in it. The fibrous capsule was made up partly of new fibrous tissue growth and partly of condensed lung parenchyma. Within this there were numerous masses of lymphocytes and masses of pigment-filled macrophages.

Pathologic diagnosis was fibrous and calcareous nodule of the lung; tuberculosis.

When last seen, seven months postoperatively, the patient was doing well and the lung remained clear.

SUMMARY

In the so-called "coin" lesion a definitive confirmed diagnosis cannot usually be reached by various laboratory and x-ray procedures. Surgical exploration for removal of the nodule and pathologic study is urgent. These lesions then—many of which look almost exactly the same on the x-ray film—will finally be diagnosed as a large variety of pathologic entities.

The important fact, however, is that in various series from 15 to 30 per cent of such lesions are malignant, and in some specially selected older age groups as high as 70 per cent are shown to be malignant. The presence of calcium in the lesion does not completely rule out the possibility that the lesion may be malignant, and it is not a contraindication to exploratory thoracotomy.

Exploratory thoracotomy, in proper hands, is a benign procedure. It should be thought of in the same way as most physicians and even the general public have been educated to think

about biopsy of a breast nodule. The nodule in the lung should be removed, so that a definite pathologic diagnosis can be made. The lesion should not just be watched for changes or even until an extensive clinical diagnostic workup can be done, for by that time, if malignant, metastases may well be present and the chance for successful surgery has generally been lost.

Carcinoma of the lung is becoming more of a public health and clinical problem. Agreement on the need for prompt exploratory thoracotomy to achieve a definitive pathologic diagnosis of such "coin" lesions is becoming almost universal among physicians skilled in treating diseases of the chest. However, such agreement is not yet so widespread among the general medical profession, and certainly not among the general public. We must keep emphasizing the need for a very prompt and direct surgical approach in diagnosing and treating such "coin" lesions if we are to reduce the present extremely high mortality from carcinoma of the lung.

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Solitary Circumscribed Pulmonary Lesions

DIAGNOSIS AND MANAGEMENT

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IT is hardly necessary to emphasize the importance of the solitary circumscribed pulmonary lesion because most physicians have learned from the recorded experience of others or from their own practices that this lesion cannot be regarded lightly. It is imperative that the nature of every such lesion be determined, either by clinical investigation or, if that fails, by examination of the tissue after surgical removal. The types of lesions which make this subject of vital importance are summarized in Figure 1; these are infectious granuloma capable of dissemination, potentially malignant tumor and carcinoma of the lung. The great majority of solitary circumscribed lesions fall into one of these three categories. Usually these dangerous lesions are indistinguishable clinically and require removal for diagnosis. However, in the enthusiasm for resection one should not forget that judicious individual consideration is always the basis for sound medical practice and may spare many of these patients an unnecessary operation.

In reviewing the literature on the subject of the solitary circumscribed lesion, one is confused by the difference in definitions. Some limit the study to patients without any symptoms while others do not. Some restrict their cases to those in which the lesion is of an arbitrarily specified size. Some weight their reports with a large number of younger patients while others weight them with older patients. All of these factors necessarily lead to statistical disagreement. In spite of this confusion, one thing remains clear—everyone reports that a significant number of solitary circumscribed lesions are malignant. Also very important, though somewhat less impressive, is the still larger number of granulomas, some of which are potentially dangerous to health and deserve serious consideration. From the practical standpoint, a suitable working definition of the solitary circumscribed lesion is as follows: It is a lesion seen on roentgenogram as a solitary one, as being completely within the substance of the lung, as being more or less rounded in shape, as having a fairly well defined border, and as being not necessarily asymptomatic but free of complications such as pleural effusion, obstructive pneumonitis or cavitation.

OBSTACLES TO CLINICAL DIAGNOSIS

Unfortunately there are many limitations to the clinical diagnosis of solitary circumscribed lesions. Most of them are peripherally placed beyond the limits of bronchoscopic visualization. Therefore bronchoscopy is only helpful in selected cases. In granulomas due to tuberculosis, smears of sputum seldom demonstrate the organism, and cultures of sputum and gastric contents do not often give positive results. If there is a question of malignancy, one is not justified in waiting several weeks for the results of cultures for the tubercle bacillus. Thus the need for haste in itself limits clinical diagnosis. The cytologic examination of sputum and bronchial secretions never gives positive results in adenoma of the bronchus, and in only a small portion of the peripherally placed carcinomas does such examination give positive results whether the tumors be primary or metastatic. Skin sensitivity tests also are of limited value, as will be seen later. The usual laboratory procedures are of little help except in evaluating the patient's general condition. Roentgenographically, there are few distinguishing characteristics by which these lesions can be differentiated, and about all that one can say is that a lesion is present, that it has a certain location within the lung and that it does or does not appear to contain calcium.

These obstacles are sufficient to prevent making a clinical diagnosis in the majority of cases, necessitating surgical removal of the lesion for more definitive information.

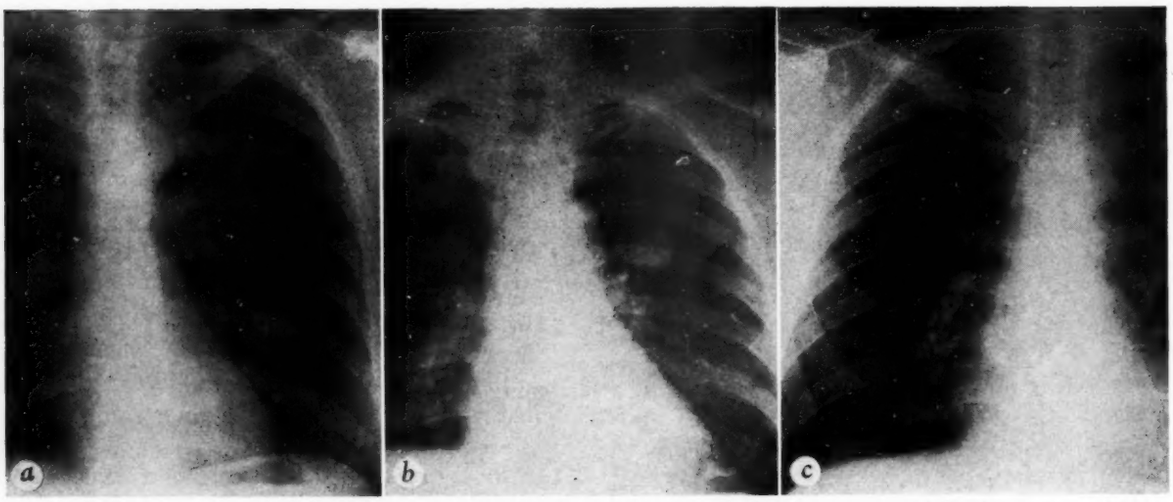

FIG. 1. Types of lesions that make the subject of solitary circumscribed pulmonary nodules important. (*a*) infectious granuloma (tuberculosis) capable of dissemination; (*b*) potentially malignant tumor (adenoma); (*c*) carcinoma of the lung.

EXTRAPULMONARY SHADOWS SIMULATING INTRAPULMONARY MASSES

In order to avoid embarrassing errors, exact localization of these roentgenographic shadows is required. Stereoscopic roentgenograms taken in the postero-anterior projection plus a single roentgenogram taken in the lateral projection are generally sufficient.

Superimposition of the shadows of lesions not within the lung may resemble intrapulmonary masses. Included in this category are tumors and moles of the skin, a solitary nipple, tumors of the thoracic wall such as osteochondromas of the ribs, callous formation at the site of rib fractures and intercostal neurofibromas, and pleural lesions including encapsulated fluid or empyema, fibrous mesothelioma and pleural plaques.

SIGNIFICANCE OF CALCIFICATION

The presence of calcification in a lesion is about the only definite evidence of benignity available in the clinical investigation of solitary pulmonary nodules. When calcium appears to be present, the physician must be sure that what he sees is calcium, that it lies within the lesion and that it is not just one of a great many such calcified areas in the lung. Where many calcific shadows are present, just by chance one might be enveloped in a malignant tumor. Postero-anterior and lateral Bucky roentgenograms or tomograms of the lesion may be very helpful in delineating calcium within the area in question, if it is not seen on routine roentgenograms.

Calcification may occur in a number of different pulmonary conditions which produce solitary circumscribed nodules: in old tuberculous foci, in hamartomas, in hematomas, around foreign bodies, within parasites, in granulomas, notably those of coccidioidomycosis and histoplasmosis, in metastatic osteogenic sarcoma, and perhaps very rarely in an adenoma of the bronchus. It does not occur in solitary circumscribed primary bronchogenic carcinoma except in those rarest of instances when a carcinoma might develop around a pulmonary stone. One is reasonably safe then in concluding that a pulmonary lesion is not malignant if it contains calcium. For the most part, calcified lesions do not have to be removed. Some of the calcified lesions yield positive cultures for tubercle bacilli and therefore are a potential source of danger. Although they have been known to rupture and discharge contents infected with tubercle bacilli, it must be unusual for this to happen. Laminated lesions perhaps never require removal as they are said to be sterile.[9] Laminations, of course, indicate a granulomatous lesion, never a tumor. Hamartomas, being strictly benign, may be treated as are other calcified lesions and allowed to remain.

THE SOLITARY CIRCUMSCRIBED LESION

Vascular Abnormalities. Very few of the vascular lesions are ever solitary and circumscribed. Arterial and venous aneurysms are

nearly always contiguous with the hilum and, therefore, are not discrete lesions. The author has seen one venous aneurysm, however, which conformed to the definition of this subject.

Pneumonitis, Abscess, Infarction and Hydatid Disease. Acute or chronic pneumonitis may occasionally give a circumscribed shadow as seen on the roentgenogram. The history should lead one to suspect such a condition and repeat roentgenograms taken after a short interval are likely to show changes in the contour of the shadow identifying it as pneumonitis rather than a tumor. Acute and chronic abscess of the lung may also produce a circumscribed shadow. Pulmonary infarction is a very common condition which may at times produce a discrete lesion. Here the history of previous operation or injury, or recent thrombophlebitis would cause one to suspect it and perhaps avoid an unnecessary operation at considerably increased risk. Roentgenograms taken after a short interval will reveal changes that remove the lesion from the tumor category. Echinococcosis is a rare entity in the United States; but when it occurs, it is likely to present in the form of a solitary circumscribed lesion.

Granulomas. The granulomas are the largest single group under consideration here. Various investigators of the subject of the solitary circumscribed lesion have reported the frequency of granulomatous lesions as follows: Grow and co-workers, 49 per cent; Abeles and Ehrlich, 20 per cent; Storey and co-workers, 70 per cent; Effler, 50 per cent; Hood and co-workers, 41.7 per cent; Sharp and Kinsella, 40 per cent; O'Brien and co-workers, 38 per cent; and Davis and Klepser, 25 per cent. The frequency of these lesions is thus well established, but their relative importance is not so well defined. It is known that they may break down and disseminate the infection causing them, but how often this happens is not clear.

The different types of granuloma can be differentiated from each other only by identifying the causative organism or substance. By microscopic examination of the tissue alone one can identify only some of the cases of histoplasmosis, coccidioidomycosis, actinomycosis and oil granuloma. Tubercle bacilli may be simulated by other acid-fast organisms and debris, hence their identity must be confirmed by culture or guinea pig inoculation in any event. It is rather useless, therefore, to spend time in search of acid-fast organisms in tissue sections.

One cannot emphasize too strongly the importance of complete bacteriologic examination of granulomatous tissue removed at operation. This investigation is fully as important as the microscopic examination of tumor tissue and should be so regarded by all surgeons and pathologists handling specimens of resected lung. Bacteriologic studies should include (1) microscopic examination of direct smears and fixed sections for fungi and other causative agents, (2) culture for tubercle bacilli, fungi and other organisms and (3) guinea pig inoculation. In spite of adequate bacteriologic examination, however, the majority of these granulomatous lesions do not yield any organisms and, therefore, their exact cause remains a mystery. Histologically they may appear to be "burned out" granulomatous infections, but some of the sterile lesions seem to be histologically active. It is not reasonable to assume that they are all due to any specific infection, such as tuberculosis, without having adequate proof of such infection and it is therefore a mistake to refer to unproved lesions as "tuberculomas."

What part do the specific skin tests play in the diagnosis of the circumscribed lesion? They are certainly a matter of interest to anyone working on this subject, but from the practical standpoint they really contribute little. It is dangerous to allow a positive or negative skin reaction to influence one in choosing between observation or exploration of this type of lesion. One must remember that the benignity of the lesion must be established beyond question or a confirmed diagnosis made. Therefore, one cannot rely on presumption, which is all that is contributed by a skin test.

Because some non-calcified granulomatous lesions are potentially dangerous (and one cannot tell beforehand which ones are), and because many of them cannot be distinguished from malignant tumors, it is necessary to remove most of them surgically. Certainly the potential dangers of leaving them in the lung outweigh the risk of present day thoracotomy. As discussed previously, calcified granulomas are much less hazardous and not all of them require removal.

Benign Tumors. Could one be certain of the identity of benign tumors they could, of course, be left alone unless they should enlarge or cause symptoms, but unfortunately it is

seldom possible to determine that a lesion is a benign one, such as a bronchogenic cyst or hamartoma; even a bronchogenic cyst may at times undergo malignant degeneration. Therefore, the majority of benign lesions have to be removed to prove their innocence. A hamartoma in which calcium is demonstrable may be managed as are other calcified lesions.

Adenoma of the Bronchus. Most adenomas of the bronchus are centrally placed and visible bronchoscopically. Moersch and McDonald found 91 per cent in that category. However, occasionally one is peripheral, solitary, circumscribed and beyond bronchoscopic visualization. Although relatively benign, between 5 and 10 per cent of them metastasize, making them a real danger. Because they are covered with intact mucosa, they do not shed tissue, so that no cells are found on examination of sputum or bronchial secretions. Preoperative diagnosis is, therefore, almost impossible when they are peripheral. Bronchial adenomas may remain unchanged for a number of years. It is not advisable, therefore, to defer thoracotomy on the basis of the fact that the lesion has remained unchanged for a long time.

Hood and co-workers found that 7.7 per cent of the solitary circumscribed lesions they studied were adenomas. Sharp and Kinsella reported two adenomas among ninety-six such solitary lesions, and Abeles and Ehrlich reported one among twenty-one. It is seen, therefore, that adenomas account for a significant, though not large, number of the circumscribed lesions under discussion. Their removal is, of course, indicated.

Primary Malignant Tumors. The high frequency of occurrence of malignant tumors makes this subject important. The proportion of the tumors that are malignant has been given by various authors as follows: Grow and co-workers, 23 per cent; Abeles and Ehrlich, 33 per cent; Watson, 40 per cent; Overholt, 24 per cent; Harrington, 23 per cent; Hood and co-workers, 35.3 per cent; Davis and Klepser, 55 per cent; O'Brien and co-workers, 42.9 per cent; Fink, 33 per cent; Sharp and Kinsella, 27.3 per cent; Storey and co-workers, 17.5 per cent; Effler and co-workers, 16.6 per cent; and Effler, 37.5 per cent. Age has a dominant relationship, the lowest incidence of malignancy occurring in the series reported by Storey and Effler and their co-workers,[4,14] in which young males predominated.

The diagnosis may be made preoperatively in some cases. Hood and co-workers were able to identify malignant cells when they were looked for in the sputum of 53 per cent of their patients. This is considerably higher than previously believed possible and indicates the value of this procedure. However, it is important to remember that the inability to find malignant cells in the sputum or bronchial secretions does not in any way eliminate the possibility that the lesion is malignant. Bronchoscopically, few of these lesions are visualized and, therefore, biopsy proof is seldom forthcoming.

A number of malignant lesions have been observed to remain the same size over a period of several years. For this and other obvious reasons there is no place for a "period of observation" or slow diagnostic methods such as cultures for tubercle bacilli when there is a possibility that the lesion is malignant.

There has been much discussion of the size of the lesions and some investigators have limited their study to lesions of specified dimensions. Because such restrictions are arbitrary, they serve little purpose. Every larger malignant tumor was once less than 2 cm. in diameter and that would have been the time to remove it. It is well known that metastatic lesions of less than 2 cm. in diameter are clearly visible roentgenographically, and therefore one should also see primary tumors of that size. The fact is, however, that a primary malignant growth of that small size is not detected. Is it because of failure to recognize small malignant tumors or because of failure of the roentgenogram to show them? Until further information is available, it is not safe to assume that a lesion of less than 2 cm. is not malignant.

The appearance alone does not distinguish between a primary and a metastatic lesion of the lung. It is necessary, therefore, that each be explored in the hope that it will prove to be curable.

Although age and sex bear a significant relationship to the incidence of the different pulmonary conditions, they do not give a sufficient basis for the management of a solitary pulmonary nodule. Primary bronchogenic carcinoma is rarely seen in persons less than thirty years of age but other types of malignancy may occasionally be encountered. Nor can the possibility of a malignancy be eliminated be-

cause the patient is a woman, although the incidence of primary cancer of the lung is much higher among men.

With all the interest in the subject of the solitary pulmonary nodule, it is surprising that there is a lack of follow-up studies on the patients with malignant lesions for whom resection has been performed. It has been assumed that resection for these lesions accomplishes its purpose. This assumption is not justified until statistical studies indicate that removal of the malignant tumor brings about a permanent cure in a significant number of patients.

Solitary Metastatic Nodules. As mentioned previously it is seldom possible to tell clinically whether a circumscribed lesion is primary or metastatic. Evidence of malignancy elsewhere in the body or the history of a previously removed cancerous lesion is very strong presumptive evidence of the metastatic nature of the lesion in question. Even after examination of the surgical specimen the pathologist is often unable to tell whether a primary or metastatic lesion has been removed.

As in any case in which surgical treatment is contemplated, a thorough general examination should be conducted; and if there are any clues to a possible hidden malignancy, they should be investigated. It is not worth while, however, to undergo exhaustive tests in a blind search for primary malignancy without any leads to follow.

If a patient has had a previous malignant lesion and then presents a solitary circumscribed nodule in the lung, the chances are strong that the pulmonary lesion is metastatic, but the finding is by no means conclusive—an unrelated disorder or even a second malignant tumor may have developed. Under favorable circumstances and after careful individual consideration, one may be justified in recommending thoracic exploration for this situation. In some instances, even though metastasis appears almost certain, one may consider thoracotomy after giving due consideration to the location and type of the original malignant tumor, its growth and invasive characteristics, the lack of evidence of metastasis elsewhere in the body, and the age and general condition of the patient. Such exploration is justified by the possibility that the lesion is not metastatic and by the fact that some patients remain well for a number of years after removal of a known metastatic growth. Cases in which this procedure is justifiable do not occur frequently, however.

CONCLUSION

In the management of the solitary circumscribed pulmonary nodule, one must prove the lesion to be benign or it should be removed. The only clinical criterion for benignity is the demonstration of calcium in the lesion. Thoracotomy, because of the low risk and short period of incapacity for the patient, is now a very useful, frequently employed, diagnostic measure and in no situation does it serve better than in the management of the solitary circumscribed pulmonary nodule.

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The Importance of Surgery in the Management of the Pulmonary Coin Lesion

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A considerable literature and even greater clinical experience has accumulated since attention was first focused on the varied nature of the pulmonary coin lesion. The main purpose of this paper is to discuss the present day management of such lesions.

The Incidence of Various Pathologic States

As far as we know, Graham and Singer[1] in 1936 made the first reference to the removal of rounded lesions within the lung. These were apparently all of tuberculous origin. In 1948, one of us (W. M. T.) reported a series of twenty-one patients,[2] giving the incidence of the various pathologic states. (Table I.) It is interesting to note the close similarity between this series and Table II which represents 714 isolated round lesions collected from the literature by Jones and Cleve.[3]

Table I

Pathologic Diagnosis	No. of Patients	Percentage
Bronchogenic carcinoma	8	38.0
Sarcoma	1	4.9
Tuberculoma	8	38.0
Cyst	1	4.9
Abscess	2	9.5
Chondroma	1	4.9
		100.2

Table II

Pathologic Diagnosis	Percentage
Malignant tumors	35.8
Inflammatory	40.0
Benign tumors	12.5
Heterogeneous group of lesions	12.5

Diagnosis

The most difficult problem in the management of any disease is the formulation of a correct diagnosis. Especially is this true in the case of the small isolated lesion within the lung parenchyma whose presence can be detected only by x-ray.

Since a goodly percentage of small rounded lesions within the lung are granulomas of various types, the appropriate skin test reactions are often employed. Probability that a specific granulomatous process is not present, as indicated by negative skin tests, is of value in that it strongly suggests that the lesion may be tumor, either benign, primary malignant or metastatic. A positive reaction, while pointing to the possibility that the pulmonary lesion may represent the granulomatous form of either tuberculosis or one of the fungus diseases, should not give the physician any special assurance that the disputed mass is not tumor. Since in so many cases the skin tests are far from diagnostic we have come to place little value upon them.

The x-ray, while of considerable worth in revealing the mass within the lung, has not proved of great value in determining its true pathologic nature. A smooth, well circumscribed border has often been considered a sign that the lesion was benign, while a roughened border which tended to streak into the normal lung tissue has been interpreted as a sign of malignancy. Basically these maxims are correct, but undue reliance cannot be placed upon them in the individual case. As an example take the widely held view that calcification within the lesion is a sign of a benign process. We have seen three instances of pulmonary carcinoma with x-ray evidence of calcium within the mass. Fibrosarcoma may also

reveal evidence of calcification. When the solitary rounded tumor is first seen, it is often wise to resort to a survey of other body systems to determine if the lesion may be metastatic.

TREATMENT

It becomes obvious that there is no reliable diagnostic pattern by which the true nature of the rounded isolated pulmonary tumor can be determined. It has frequently proved disastrous to treat such lesions by periods of observation ranging from several weeks to many months. It will be recalled that Graham and Singer, in a day when pulmonary resection was far from a safe procedure, attacked such lesions with boldness. The wisdom of their early approach has been amply proved in the many subsequent studies showing the high incidence of malignancy in these lesions. It has become our custom to remove all such lesions, unless (1) it is known to have been present over a period of many years, or (2) it can be shown that it represents merely one of multiple metastases. In situations other than the foregoing thoracotomy is performed.

At operation, if gross or frozen section examination reveals the presence of carcinoma, lobectomy or pneumonectomy is performed. At the present time there is considerable discussion as to the relative merits of lobectomy and pneumonectomy in the treatment of pulmonary malignancy. In the absence of evidence of glandular involvement beyond the point of lobar drainage it has been fairly well demonstrated that lobectomy is as efficacious as pneumonectomy. The question of the so-called radical pneumonectomy might be raised, but it is doubtful whether many persons know what a radical pneumonectomy really is. It would seem to the authors that a bronchogenic carcinoma, in a period of active growth, is equally as well treated by lobectomy as pneumonectomy, since it is extremely doubtful that it can be circumvented during this phase of its life cycle. It is the belief of one of us (W. M. T.) that those carcinomas of the lung which are cured are removed during a period of relative cellular inactivity.

We have dealt with benign lesions by either removal of the segment in which they are contained or by local enucleation. We have not resorted to the so-called wedge clamp method. For some peculiar reason the vast majority of benign tumors and granulomatous lesions appear upon the lobar surface. Thus they are rather easily removed by an enucleation procedure, similar to removal of a thyroid adenoma, in which the individual vascular and bronchial elements are clamped, divided and ligated as encountered. No attempt is made to close the defect thus created since, when this is done, in the human or in the experimental animal the formation of air containing cysts or fibrosing hematomas occasionally occurs.

In all patients the chest is drained for a period of twenty-four hours with either one or two intercostal tubes, and with or without suction depending upon the individual surgeon's fetish in this matter.

COMMENTS

It should be obvious that any rounded object resembling tumor within the parenchyma of any organ is best treated by removal. In this era when great propaganda campaigns are being carried on for the early detection and treatment of cancerous and pre-cancerous conditions it does not seem feasible to advocate a policy of watchful waiting on lesions which have a 38 per cent chance of being malignant. Undoubtedly many persons have lost their lives because their physician has felt justified in watching a rounded mass to determine whether it will increase in size. The growth of the primary tumor has nothing to do with its metastatic potentialities. The authors have recently seen an individual who was observed over a period of ten years with a slowly growing tumor of the left lower lobe. The bearer of the lesion was finally convinced that its removal was essential, and on microscopic section it proved to be adenocarcinoma. Whether this lesion originally was an adenoma is, in our opinion, beside the point since we believe that adenomas are actually adenocarcinomas. It seems probable that the relative malignancy of an adenocarcinoma is quite as difficult to evaluate as whether a cartilaginous tumor is a chondroma or a chondrosarcoma. It is likely that much depends upon the section of the tumor that is removed for study.

Metastatic lesions in the lung have been removed on numerous occasions. The results which have been accomplished in some of these patients has been most gratifying. It would seem that the best results have come in those patients in whom the metastatic lesion appeared at a considerable interval of time after

the removal of the primary growth. It is the experience of all thoracic surgeons that there is an increasing gradient of good results as the time lapse increases between the removal of the primary and the appearance of its secondary manifestations. He who advises against the removal of a solitary, probably metastatic, nodule occurring over one year after the removal of the primary, assumes a heavy responsibility.

For many years the feeling has been prevalent that thoracic exploration is a perilous method of arriving at a diagnosis in pulmonary disease. Many physicians would advise that their patients be denied thoracic exploration while giving willing assent to an exploration of their peritoneal cavity. In a day of competent anesthesia and surgery such reasoning shows a fundamental ignorance of the facts. Exploratory thoracotomy today can be performed with a safety at least equal to that of exploratory laparotomy, and therefore flings wide the portals to the problem of the undiagnosed solitary pulmonary lesion.

The preceding paragraph is pertinent as we approach the consideration of the 60 to 65 per cent of rounded pulmonary masses whose pathologic nature will prove to be either benign or inflammatory.

Benign tumors of the lung, such as chondromas, fibromas or hamartomas seldom become malignant. It is often difficult, however, to say whether a chondroma is truly a chondroma or a chondrosarcoma. Most of these pathologic states appear the same by x-ray, and there are no diagnostic methods to distinguish between them. Therefore, all must be removed.

The rounded inflammatory mass within the lung has long been diagnosed by the pathologist as a tuberculoma, because it was caseating at its center and laminated at the periphery. Many individuals have believed that the so-called tuberculoma was an innocuous lesion. Recently Mitchell[4] has shown that in untreated patients there is about one chance in four of the progression of such a lesion or its evacuation into the tracheobronchial tree with widespread dissemination of the disease. A similar observation was made by Mathers[5] who found that, over a period of five to ninety months, twelve of twenty-three tuberculomas either enlarged, cavitated or showed evidence of parenchymal spread. Thus it would appear that the so-called harmless tuberculoma can on occasion prove quite noxious.

Occasionally caseous lesions are found from which the tubercle bacillus can be grown, but in the great majority of the so-called pulmonary granulomas no tubercle bacilli can be demonstrated on smear or microscopic section, nor can they be grown on culture. Recently Puckett[6] has shown, in a study of such lesions from the Fitzsimons General Hospital, that many of these patients actually suffered from a granulomatous form of histoplasmosis. Brosius[7] has confirmed this study in a group of our own patients at Harper Hospital. It is becoming increasingly evident that histoplasmosis can become a generalized fatal disease. It would not, therefore, seem unwarranted to remove such potentially dangerous lesions.

CONCLUSION

The problem of the benign appearing, "harmless," round lesion of the lung has been reviewed.

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Benign Tumors of the Bronchus and Lung

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ALTHOUGH the occasional benign tumor of the bronchus and lung was recognized in former years, chiefly at necropsy, it was not until comparatively recent years that these tumors were treated surgically. Sutton, in his book on "Tumors—Innocent and Malignant" published in 1894, fails to mention benign tumors of the lower respiratory tract. In Kaufmann's monumental work on pathology there are several references to these tumors, but only one antedating the work of Sutton. In 1930 Patterson published a paper on benign bronchial neoplasms, reviewing twenty-six cases gleaned from various sources. Sixteen of these tumors were diagnosed via bronchoscopy and ten at necropsy. Two years later Wessler and Rabin reported on seventeen benign bronchial tumors seen at Mount Sinai Hospital in New York City. In the combined series of forty-three cases reported in the latter two papers there were fifteen adenomas, nine fibromas, seven polypi, three chondromas, three lipomas, two fibrolipomas, and one each of papilloma, granuloma, lymphoma and aberrant thyroid.

In a number of cases of benign tumors of the lower respiratory tract published prior to 1935 removal was accomplished via the bronchoscope either by snipping it out of the bronchial wall or by cauterization of the tumor. However, it was not until about twenty years ago that such a tumor was removed via the transthoracic approach. In 1935 Andrus reported that in the files of the Chest Tumor Registry of the American Association for Thoracic Surgery there were 155 case reports but not a single one was for benign tumor of the bronchus or lung. The relatively large number of such cases reported in recent years may be ascribed to our advances in radiology, endoscopy, pathology, anesthesia and thoracic surgery. The advent of mass chest x-ray surveys in recent years has greatly increased our awareness of asymptomatic pulmonary tumors, a goodly percentage of which have been shown to be malignant and a lesser percentage benign. Although such roentgenographic studies give the first clue of the presence of a tumor, it is not until the tumor tissue is examined by the pathologist that one can venture an opinion as to whether the tumor is malignant or benign.

The object of this paper is to review the subject of benign bronchopulmonary tumors, to present a classification of such tumors, based upon the one proposed by Liebow, and to present cases illustrative of some of these tumors.

The present classification of benign bronchopulmonary tumors is based upon the genesis of the lung and bronchial tissues. It does not propose anything new, but it does attempt to organize the available material on the subject. To this end it was found expedient to subdivide these tumors according to their origin. Thus they are either epithelial, mesodermal or developmental in origin.

Epithelial Tumors
1. Papilloma of the bronchus
2. Adenoma of the bronchus

Mesodermal Tumors
1. Vascular tumors
   (a) Cavernous vascular tumors
   (b) Capillary hemangiomas
   (c) Vascular endotheliomas
2. Intrabronchial tumors
   (a) Fibroma
   (b) Chondroma
   (c) Lipoma
   (d) Leiomyoma
   (e) Myoblastoma
   (f) Plasmacytoma
   (g) Lymphoma

3. Peripheral tumors of the lung
   In addition to those listed above as "intrabronchial tumors" the peripheral lung tumors include:
   (a) Neurogenic tumors
   (b) Xanthomas

Developmental Tumors

1. Hamartoma
2. Teratoma

PATHOLOGY

Epithelial Tumors. 1. The *papilloma* of the bronchial tree is often an inflammatory lesion and therefore not infrequently of multicentric origin. True non-inflammatory papillomas of the bronchus are very rare. The papilloma most often occurs in the region of the stem bronchus. Grossly, it is a firm, coarse, sessile, polypoid or cauliflower-like mass which projects into the lumen of the bronchus. Microscopically, it is comprised of small stratified cuboidal or squamous epithelial cells about a stalk of connective tissue. Keratinization is quite common in these tumors. The surrounding tissues of the bronchial wall are not invaded by the tumor.

2. The *adenoma* is the most prevalent of the benign tumors of the bronchus and lung. It is said to constitute about 8 per cent of all primary tumors of the lower respiratory tract and about 80 per cent of all the benign tumors in this part of the body. It is a slowly growing local tumor, at first circumscribed but later invasive or sluggishly metastasizing. Because of this potentiality, Hood, Good, Clagett and McDonald (1953) consider this tumor to be malignant. Most frequently, the adenoma involves the subepithelial tissues of the larger bronchi. However, it may also arise from the smaller bronchi within the substance of the lung. There are several theories as to the origin of these tumors. Some subscribe to the view that they arise from the bronchial mucosal glands; others believe that they arise from a special group of cells known as the oncocytes frequently seen in the bronchial glands. Womack and Graham contend that these tumors arise from persistent embryonal bronchial buds; Churchill endorses the view that they arise from vestigial pulmonary lobes growing within the bronchus; and others believe that they arise from the bronchial lymphoid tissues. The most widely accepted view is that they arise from the bronchial glands and their ducts.

There are two well differentiated histologic patterns seen in these tumors: (1) the carcinoid form and (2) the cylindroid form. The carcinoid form of bronchial adenoma is the more common, constituting about 85 per cent of the adenomas. Grossly, these tumors project into the lumen of the bronchus as a smooth, pinkish grey, globoid or lobulated mass, the surface of which is often covered by many fine vessels. Very commonly these tumors grow partly extrabronchially, too. Jackson and Jackson (1950) point out that in the early case the tumor is sessile but later it may become pedunculated. The consistency of these tumors is variable. The softer tumors are pale pink while the firmer tumors are pale brown or tan. (Fig. 1.) Microscopically, these tumors consist of an outer thin sheet of bronchial epithelium in which metaplasia has taken place. Beneath this layer there is a thickened reticular basement membrane and dense connective tissue. Deep to this is the true neoplastic tissue which characteristically consists of uniform small cells with finely granular acidophilic cytoplasm and nuclei that are finely stippled with chromatin. These cells are arranged in sheets or collections resembling acinar groupings. In the invasive stages the cells are less uniformly distributed but the basic pattern of localization remains unaltered. Mitosis is very rare in these tumors. Bone formation is occasionally seen in the adenoma and is believed to be due to metaplastic changes in the cartilage or osseous transformation of the septa of the capsule about the tumor.

In general, the truly peripheral adenoma is structurally the same as the endobronchial type. (Fig. 2.) However, in these tumors the component cells are more granular and more variable in size and shape.

A variant of the carcinoid form of bronchial adenoma is the oncocytoid adenoma. Grossly, they have most of the features of the other tumors but are firmer in consistency and pale tan in color. Microscopically, the predominating cell is quite large; the cells are packed closely together, the stroma is not abundant, and vascular channels are inconspicuous. The cell characteristic of this tumor has a granular or striated cytoplasm and a small centrally placed nucleus which resembles the bronchial mucous glands of older patients.

FIG. 1. Right lung removed surgically for adenoma (carcinoid) of the intermediate bronchus. Same case as Figure 15.

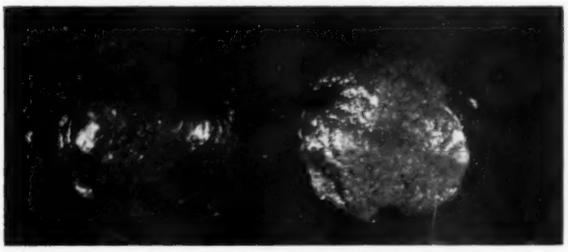


FIG. 2. Enucleated adenoma (carcinoid) of the left lung. Same case as Figure 9.

Adenomas comprised entirely of oncocytoid cells are rare. However, Stout (1943) reported such a case. Most often these cells occur in groups within a carcinoid and are separated from the remainder of the tumor by connective tissue. At times these cells comingle with the carcinoid cells, in which instances transitional cells may also be seen.

The cylindroid form of bronchial adenoma comprises about 15 per cent of all bronchial adenomas. It arises from the same cell as does the carcinoid. Grossly, this tumor is pale yellow, fairly firm and more translucent than the carcinoid. The cut surface of the cylindroid is usually moist, having the appearance of thin mucus. The tumor is often lobulated and extends diffusely along the bronchial wall. (Fig. 3.) If a capsule is present, it is usually indistinct. Microscopically, the cells comprising this tumor are pleomorphic and of the epithelial variety. The cells are usually smaller than those seen in the carcinoid and are more basophilic. The nuclei are variable in size and often fusiform in shape. The cells are usually arranged in the form of branching cylinders or tubes lined by a double layer of cells in a plexiform, honeycombed mass. Mitoses in these cells are fairly common. The stroma in these tumors is a loosely arranged connective tissue which is much less vascular than that seen in the carcinoid. The cylindroid form of adenoma exhibits a tendency toward invasion of the tissues and may even extend into the bronchial cartilages. A variant of this form of adenoma is known as the mucoepidermoid adenoma, a mucus-producing tumor in which there is an intimate admixture of well differentiated mucus-secreting cells and sheets of cells resembling squamous epithelium.

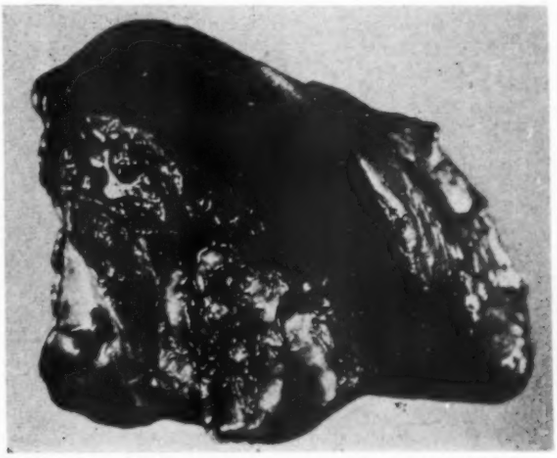


FIG. 3. Right lower lobe removed surgically for an adenoma (cylindroid) of the lower lobe. Same case as Figure 16.

Mesodermal Tumors. 1. *Vascular tumors:* (a) The *cavernous vascular* tumors are comprised of communicating, tortuous, dilated vascular channels with both venous and arterial components which have been variously described as arteriovenous fistulas, arteriovenous varices, cavernous hemangiomas, angiomas, telangiectasis and intrapulmonic aneurysms. Makler and Zion define a pulmonary hemangioma as a "knot of blood vessels connected by feeder vessels with both the pulmonary arterial and venous circulations. Thus it acts as a shunt whereby blood can pass from the arterial to the venous circulation without passing through the lungs and being oxygenated." In a review of fifty cases Giampalmo

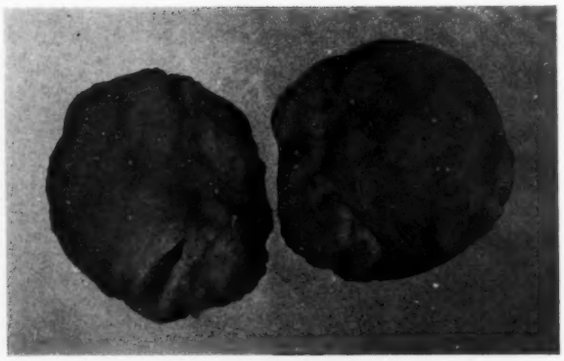


FIG. 4. Enucleated endothelioma (mesothelioma) of the right lung. Same case as Figure 10.

found that 66 per cent of the cases involved the lower lobes, 18 per cent involved the upper lobes and 16 per cent were in the right middle lobe. Grossly, these tumors are well defined within the lung either as single or multiple lesions. They may be found in any part of the lung, superficially or deeply within the parenchyma of the lung. They consist of a distended, thin-walled, afferent artery, distended efferent veins, and intervening between them are loculated vascular sacs of distended vessels. Microscopically, large spaces are noted, lined by thin-walled endothelial cells, supported by a fine connective tissue. The arterial structures are indistinguishable from the venous component. Muscle is occasionally seen in the wall surrounding the dilated channel.

(b) *Capillary hemangiomas* are rarely encountered in the bronchi or lungs. However, when present they resemble those found in other parts of the body.

(c) *Vascular endotheliomas* of the lower respiratory tract are very uncommon. Edwards and Taylor (1937) reported four such tumors. When present it is a well defined, discrete, more or less encapsulated lesion. (Fig. 4.) On microscopic examination of the tumor one notes cells which are mainly polyhedral in shape, surrounded by a well defined membrane. The cytoplasm of the cell is clear, the nucleus small, pale and vesicular, and contains several small nucleoli. Also present in these tumors are circulatory channels (vascular and/or lymphatic), the walls of which are often formed by masses of tumor cells. The cells may be arranged in whorl-like fashion and/or in groups which form columns or channels two or three cells in thickness. Giant cells are not uncommon in these tumors.

2. *Intrabronchial tumors* most often are seen

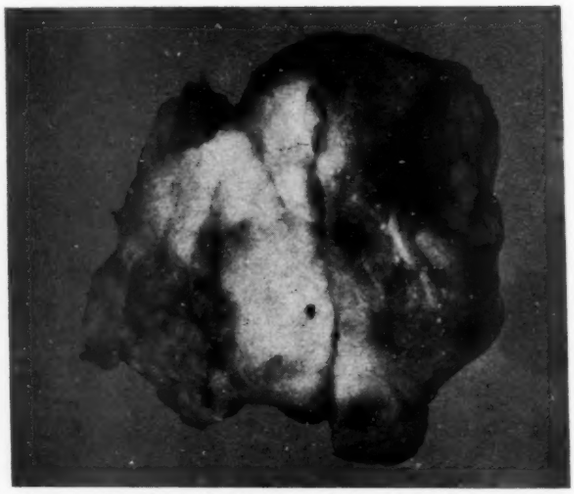


FIG. 5. Enucleated fibroma of the right lung. Same case as Figure 11.

in the more proximal bronchi but are also known to arise from segmental and subsegmental bronchi. They may be pedunculated or have a broad base in the wall of the bronchus. In the occasional instance they also penetrate the outer coats of the bronchial wall so as to form a localized tumor, part of which projects into the lumen of the bronchus and part of which extends into the parenchyma of the lung as an extrabronchial tumor.

(a) *Fibroma:* These tumors are of variable size, but most often they are small. Crimm and Kiechle report removal of a fibroma with the right lower lobe, the weight of both being 740 gm. The present writers removed a parenchymal fibroma of the lung which measured, 3 by 3 by 5 cm. Grossly, these tumors are firm, pale and either smooth or nodular on the surface, and when within the lung they are distinctly outlined against the pulmonary tissue. The cut surface of these tumors is quite similar to its outside surface. Cystic changes are occasionally seen when the tumor is transected. (Fig. 5.) Microscopically, they are composed of closely packed spindle-shaped cells. In some instances the cellular elements are less prominent and the collagen tissue more in evidence. Myxomatous changes and fatty infiltrations are also seen occasionally in these tumors.

(b) *Chondroma:* The pure chondroma is not a common tumor. In 1950 Hochberg and Pernikoff reported that seventy-eight tumors had been recorded in the literature up to that time. There are two theories as to the origin of these tumors. The first is based upon the

assumption of hyperplasia of the bronchial cartilages and the second, more widely accepted theory, of delayed development of cartilaginous elements in embryonic rests which suddenly begin to grow. The chondroma varies in size and location, the smaller ones being intrabronchial while the larger ones are within the parenchyma of the lung. Linser describes a chondroma of the lung which was 20 by 16 by 9 cm. These tumors are firm masses, round or ovoid in shape, have a lobulated surface and are covered by a semi-translucent fibrous capsule. They are distinct tumors and do not invade the surrounding tissues. The color of the cut surface of the tumor varies with its composition. When composed of hyaline cartilage, the tumor is very firm, grey-white in color and has a bluish translucency. (Fig. 6.) When these tumors contain abundant fibrous or elastic tissue, they are more opaque and have a yellow-white color. Microscopic examination of the tumor reveals nests of hyalin and fibrocartilaginous tissue separated from each other by fibrous connective tissue stroma. Histologically, these tumors simulate normal cartilage. The fibrous tissue capsule and trabeculae often contain small vessels. Within the substance of the tumor calcific deposits and rudimentary bone formation may be noted. In other instances there may be bleeding into the tumor and myxomatous degeneration.

(c) *Lipoma:* While fat is seen frequently in many lung tumors, true bronchopulmonary lipomas are very uncommon. Langston (1950) reported that up to that time there were but ten such tumors reported in the medical literature. There are numerous theories which attempt to explain the genesis of these tumors. The most acceptable one is an overgrowth of a normal constituent of the bronchus. Grossly, these tumors are rounded or lobulated, yellowish pink, semi-firm, often pedunculated, and covered by intact mucous membrane. Microscopically, these tumors are comprised of uniform, mature fat cells with moderate amounts of fairly dense fibrous tissue septa separating groups of cells into islands. In some areas lymphocytes and small clusters of tubular glands lined by a single layer of cuboidal or low columnar cells may be noted.

(d) *Leiomyoma:* This tumor, too, is rather uncommon in the lower respiratory tract. A review of the published cases shows that only seven such cases were reported in the medical literature before 1954. Franco reported a leiomyoma of the lung 13 by 11 by 9 cm., discovered at necropsy. Grossly, these tumors are grey-tan in color, spherical and firm to palpation. They are usually encapsulated and shell out readily. The cut surface is opaque with grey interlacing whorls. Areas of necrobiosis are seen frequently in these tumors. Microscopically, these tumors consist of whorls of mature muscle cells with varying amounts of fibrous tissue distributed throughout their substance.

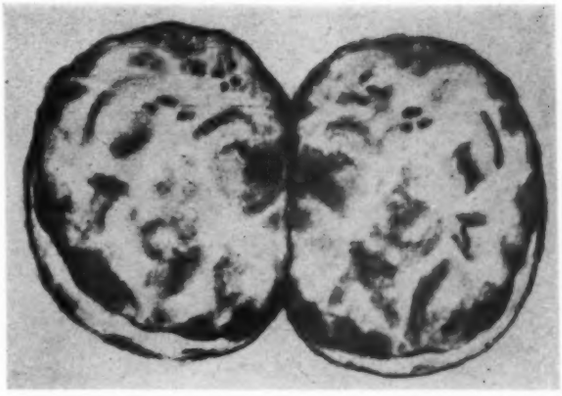


FIG. 6. Enucleated chondroma of the right lung. Same case as Figure 12. (Previously published in March 1950 issue of *Diseases of the Chest.*)

(e) *Myoblastoma:* The presence of a striated muscle tumor in this region is believed to be the result of mesenchymal tissue activity. These tumors are small, well circumscribed and fixed within the wall of the bronchus. Microscopically, they have three characteristics. The first is that they contain large cells resembling undifferentiated muscle fibers arranged in long bands with an occasional syncytial mass. The cells have a foamy, vacuolated, granular, basophilic cytoplasm, and small round to oval dark-staining nucleus. The granular structure of the cytoplasm is arranged in parallel rows. The second type of cell is represented by clumps of elongated cells resembling smooth muscle cells whose elongated nuclei have a fine chromatin network, rounded ends and nuclei. The cytoplasm is made up of longitudinal myofibrils. These cells either form prominent clumps or intermingle with the first type. The third characteristic cell is one which is elongated and has abundant cytoplasm containing eosinophilic granules and an oval dark-staining nucleus.

(f) *Plasmacytoma:* There have been but five

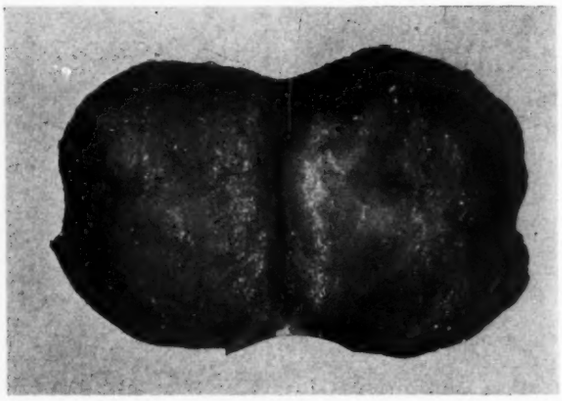


FIG. 7. Enucleated neurofibroma of the right lung. Same case as Figure 13.

such tumors reported (Hill and White, 1953). The true plasmacytoma is made up entirely of plasma cells while another form is composed chiefly of plasma cells, leukocytes, fibroblasts and some other cells. The latter form is a pseudoplasmacytoma and is not considered to be a true form. The theories of the origin of this tumor are (1) from the lymphocytes, (2) from the fixed tissue lymphocytes, (3) from the hematogenous lymphocytes, and (4) from connective tissue elements. These tumors are usually single but may also be multiple. They are usually round or ovoid in shape, and are polypoid or lobulated masses which vary widely in size. Microscopically, the predominating cell is round, oval or polygonal with abundant cytoplasm, and contains an eccentrically placed nucleus. Within the nucleus there are five to ten deeply staining blocks of chromatin arranged in a circular manner inside of the nuclear membrane. Adjacent to the nucleus there is a paranuclear poorly staining region.

(g) *Lymphoma:* These tumors are also very uncommon. They arise from the lymphoid tissue in the bronchial wall and grow into an ovoid, firm, encapsulated mass. On cut section they are whitish and contain areas resembling lymphoid nodules. Microscopically, the tumor is composed of cells of the lymphoid tissue variety in which there are large follicles with prominent germinal centers.

3. *Peripheral tumors:* Such tumors usually arise in the distal parts of the lower respiratory tract. It is often difficult to state definitely whether peripheral tumors of connective tissue origin not obviously associated with a bronchus have originated in the parenchyma of the lung, the pleura or from a minute bronchiolar subdivision. Although some believe that the leiomyoma is the most frequent tumor at this site, the relatively small number of tumors seen here does not justify any such conclusion.

(a) *Neurogenic tumors:* This is an uncommon primary tumor of the lung, only five being reported to date. Grossly, this tumor is a smooth, firm, well encapsulated, whitish glistening mass which is most often single but may also be multiple. Microscopically, it is noted that these tumors have a connective tissue capsule with septa extending from it into the tumor proper. (Fig. 7.) Two kinds of tissues are usually seen in these tumors. There is the dense, compact tissue of medium-sized spindle-shaped cells with uniform elongated oval nuclei, arranged in parallel rows. These tumors contain abundant collagen and reticulum fibers arranged in straight bundles, polarized in the same parallel axis. The other tissue is of looser texture with spindle cells in a disarranged pattern and moderately large vascular spaces surrounded by thick hyalinized walls.

(b) *Xanthoma:* Intrapulmonary xanthomas are also very rare, only two such cases having been reported to date. Grossly, it is a loosely encapsulated golden yellow tumor which can be separated readily from the surrounding tissues. Microscopically, it is composed of characteristic foam cells and contains an abundance of fat globules.

Tumors of Developmental Origin. 1. *Hamartoma:* Albrecht (1904) originally defined this lesion as a "tumor-like formation in which there is an abnormal arrangement of the normal components of that organ. The abnormality may take the form of a change in quantity, arrangement or degree of differentiation or may comprise all three phases." Two major types of hamartomas are found in the lung: (1) the adult form which is relatively a small circumscribed lesion, and (2) the infant or newborn form which is a massive, diffuse process often occupying a lobe or even an entire lung.

The adult form: These tumors are most often located in the subpleural or peripheral part of the lung and on occasions in the larger bronchi. Chardack and Waite (1953) found that only fifteen such tumors were reported as having arisen in the larger bronchi, while Young and his co-workers (1954) reported that of the approximately 200 hamartomas reported only twenty-four were endobronchial in origin. The

hamartomas vary in size from about ½ to 12 cm. in diameter. Most of the tumors are about 1 or 2 cm. in diameter. In most instances these growths are covered by a thin fibrous capsule. Externally, they are multicolored, nodular or lobular, while the cut surface is pale bluish white and often contains yellowish zones of fat deposits and calcification. (Fig. 8.) Irregular areas of cystic changes are not infrequent in these tumors. Microscopically, the tumor has communicating and interlacing masses of stroma. In proximity to these there are sheets of epithelium resembling that of the bronchial lining. The stroma consists mainly of masses of cartilage (hyaline chiefly, but also fibrous and/or elastic) which merges peripherally with the fibrous connective tissue. Within the stroma are embedded groups of fat cells, bundles of smooth muscle and areas of ossification.

The diffuse hamartoma of the newborn: This tumor is an intrauterine malformation involving a large part of a lung. Grossly, this tumor may replace the greater part of a lobe or an entire lung. Although the tumor is a circumscribed lesion, it is not encapsulated. Jones reported the case of a one day old child with such a tumor occupying the greater part of the right upper lobe. Microscopically, the tumor consists of a supporting stroma simulating bronchioles. It also contains islands of cartilage, fatty tissue, fibrous tissue and blood vessels.

2. *Teratoma:* When located within the lung it has all the characteristics of a teratoma in other parts of the body. It is an uncoordinated growth of multiple tissues, many of which are foreign to the site of origin. It is the result of a developmental aberration in which the germinal layers form various tissues into a tumor. There may be domination of one particular germ layer, but the others must also be present if one is to classify the tumor as a "teratoma."

LOCATION

The site of origin of these tumors determines its location. Most commonly they arise within the region of the proximal half of the bronchial tree, i.e., from the beginnings of the main bronchi down to and including the segmental bronchi. Less frequently, they arise distal to the segmental bronchi and in the periphery of the lung. Our choice in relating these tumors anatomically to the bronchi should not be interpreted as subscribing to the view that these tumors are necessarily always bronchogenic in origin. Any one of these tumors may arise from any region in or in proximity to the bronchopulmonary system. The papilloma and the adenoma most often arise from the medial part of the bronchial tree. Except for the small telangiectatic tumors, most of the vascular tumors arise in the outer half of the pulmonary vascular field. Most of the other tumors usually arise in the region of the middle lung field and periphery of the lung. Although most commonly the tumors in the larger bronchi grow as endobronchial tumors, a goodly percentage of them have extrabronchial extensions. The tumors in the peripheral parts of the lung may, to all intents and purposes, be considered as extrabronchial in their manner of growth. The location and manner of growth play an important role in the clinical manifestations of their presence.

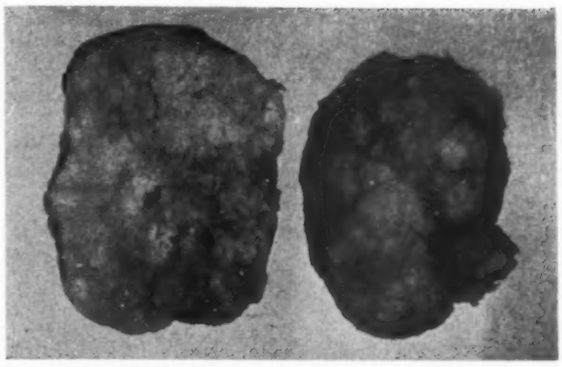


FIG. 8. Enucleated hamartoma of the right lung. Same case as Figure 14.

SYMPTOMS AND SIGNS

The symptoms and signs are variable and dependent upon (1) location and size of the tumor, (2) manner of extension, (3) histopathologic nature of the tumor, (4) duration of condition, (5) vascularity of the tumor and (6) effects upon the surrounding tissues and associated complications. Many of these tumors are completely asymptomatic and are discovered on "routine" roentgenographic studies of the chest or at necropsy. Those tumors which are endobronchial manifest their presence rather early by a cough and wheezing. This is particularly true of the tumor in the proximal part of the bronchial tree. As the tumor in this location increases in size and obstructs the bronchial lumen, it leads to impaired respiratory function and is manifest by

dyspnea, palpitation, elevation in pulse rate and possibly a reduction in the cough. However, if the obstruction to the bronchus is incomplete or intermittent, all of these manifestations are present coupled with variable degrees of expectoration and elevation in temperature. The latter condition is due to pulmonary infection distal to the obstruction. On the other hand, tumors in the same location which grow extrabronchially and even of larger size than the one within the lumen of the bronchus may remain relatively asymptomatic because they do not encroach upon the respiratory passage and do not interfere with pulmonary ventilation. By the same token, if such an extrabronchial tumor should encroach upon a large pulmonary artery or vein, it will impair pulmonary circulation and have a similar clinical effect as an endobronchial tumor insofar as the oxygen supply to the tissues is concerned.

Tumors which arise within the pulmonary parenchyma, at a distance from the larger bronchi and periphery of the lung, are notoriously free of symptoms. This is due to the fact that they do not encroach upon a large bronchus and that they grow slowly, giving the patient time to accommodate to any loss of function which may take place. Tumors arising in the peripheral parts of the lung do not encroach upon pulmonary tissue until they are very large. However, they do cause local swelling and congestion of the tissues. As a result, the visceral pleura rubs against the parietal pleura and gives rise to local pain.

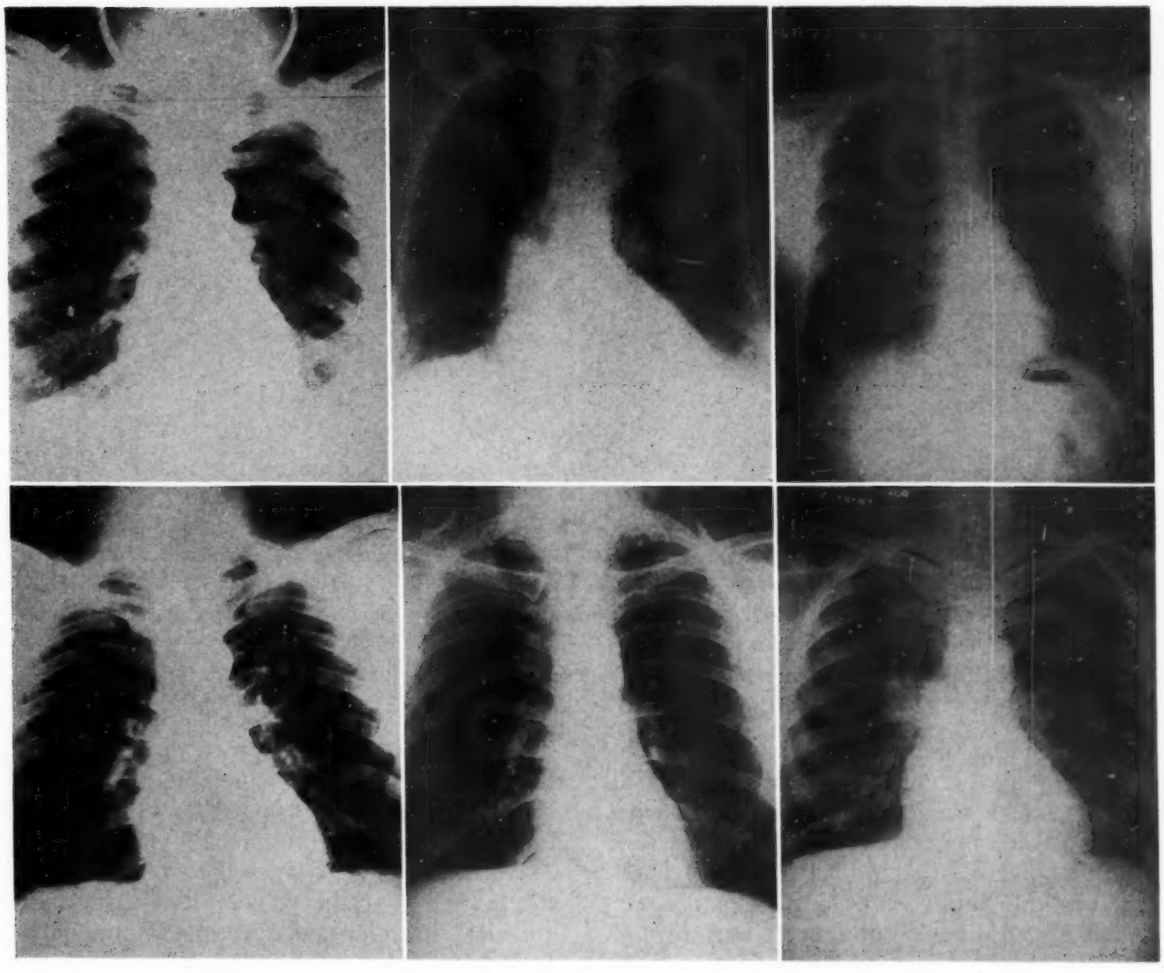
In all cases, regardless of the site of origin but more commonly in that group of cases which arise in the proximal bronchi, there is a tendency for the sputum to be blood-streaked or stained. This is due to superficial erosion and necrosis of the tumor. In other instances, as in the adenoma and vascular tumor, hemoptysis may be the first manifestation of the presence of the tumor. In some instances the bleeding is sudden in onset, brisk and profuse.

Because of their peculiar effects on physiology, hemangiomas of the lung present distinctive features which aid in their diagnosis. The passage of unoxygenated blood from the venous radicles directly into the arterial circulation, as occurs in these cases, reduces the oxygen saturation of the circulating blood. As a consequence, cyanosis and dyspnea will develop. These symptoms and signs are in direct relation to the degree of arterial blood-oxygen unsaturation. In the early stages dyspnea and cyanosis are usually absent or very mild; but as the condition progresses, they may become very distressing. Clubbing of the fingertips and toes, epistaxis and hemoptysis are not uncommon in these patients. The other signs of chronic hypoxia may also evolve. The diagnostic thoracic physical signs are a continuous blowing murmur which becomes intensified with inspiration and fades out to a soft souffle toward the end of expiration. Since this disease may involve several areas in the lung, this sign may be found in more than one region. The absence of this sign does not exclude the presence of hemangioma of the lung.

ROENTGENOGRAPHIC MANIFESTATIONS

By far the most frequently encountered roentgenographic finding in benign tumors of the lower respiratory tract is the circumscribed, well delineated opacity, especially when in the parenchyma or periphery of the lung. (Figs. 9 to 14.) However, such a shadow does not exclude the possibilities of the tumor being malignant. In those cases in which the tumor is small and/or completely within the wall of the bronchus, conventional roentgenographic studies may fail to reveal the presence of the tumor. However, when such a tumor grows into the lumen of the bronchus, it may obstruct the bronchus and cause intermittent or complete obstructive emphysema and/or atelectasis distal to the obstruction. (Fig. 15.) Similar accompanying changes may occur in cases of pedunculated intrabronchial tumors. Where obstructive changes occur, one may expect recurrent and chronic inflammatory changes in the lung. If these changes are protracted, opalescence of the lung distal to the tumor will also be noted. Such roentgenographic findings are to be expected regardless of the nature of the tumor. Occasionally, as in the case of the cylindroid adenoma, the tumor may grow along the bronchial wall and either contribute to the opacity or cast its own opacity, as in Figure 16. These roentgenographic changes in the lung are based upon the position of the tumor and not upon its histopathologic structure.

Hamartomas of the lung may be recognized occasionally on roentgenograms by the presence of calcific and cystic changes within the tumor. However, the presence of such changes is not diagnostic of a hamartoma. The caver-



9 10 11

12 13 14

FIG. 9. Circumscribed tumor (adenoma) within the parenchyma of the left lung. Same case as Figure 2.

FIG. 10. Postero-anterior roentgenogram showing a circumscribed tumor (endothelioma) in the right infrahilar area. At the time of operation this tumor was found to be in the superior segment of the right lower lobe. Same case as Figure 4.

FIG. 11. Circumscribed tumor (fibroma) within the parenchyma of the right lung. Same case as Figure 5.

FIG. 12. Circumscribed tumor (chondroma) within the parenchyma of the right lung. Same case as Figure 6. (Previously published in March 1950 issue of *Diseases of the Chest.*)

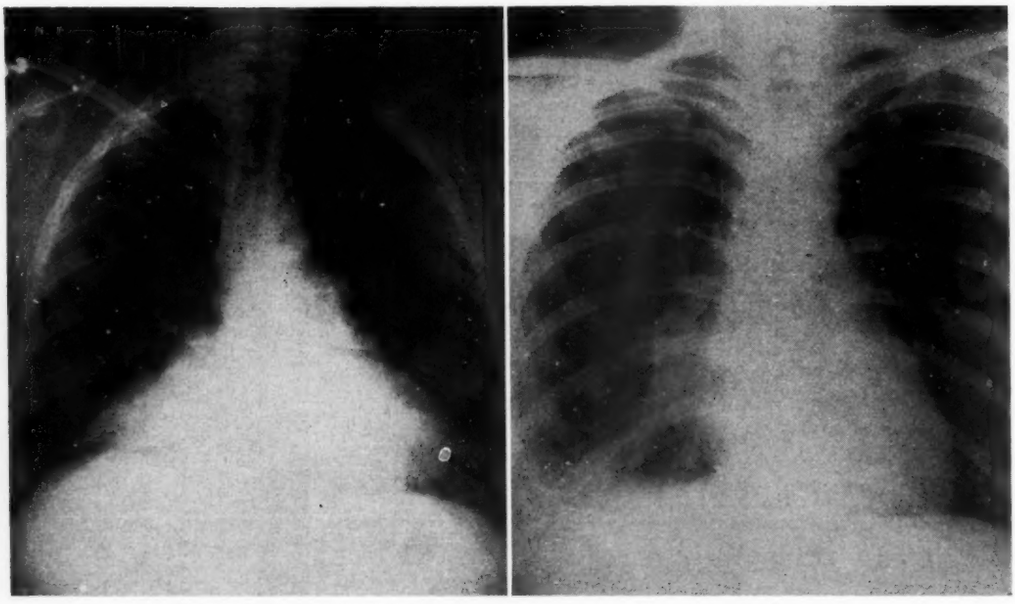
FIG. 13. Circumscribed tumor (neurofibroma) in the right suprahilar area. Same case as Figure 7.

FIG. 14. Well delineated, irregularly opaque mass in the right parahilar area. This tumor (hamartoma) was found to be in the superior segment of the lower lobe. Same case as Figure 8.

nous hemangioma may be suspected in the patient who on fluoroscopy shows the characteristic changes with the Valsalva maneuver within the area of the tumor; on laminagraphic study of the tumor area one notes worm-like configurations within the opacity and a tongue-like opacity extending from the tumor toward the hilum. Angiography is often diagnostic of this lesion.

ENDOSCOPY

While endoscopy is a valuable adjunct in the diagnosis of endobronchial tumors, the differentiation between benignity and malignancy by this modality is unreliable. In approximately half of the cases of benign tumors of the lower respiratory tract one may visualize the growth via the endoscope.



15 16

FIG. 15. Delineated opacity of the right lower lobe due to tumor (adenoma) and atelectasis. Same case as Figure 1.

FIG. 16. Opacity in the paracardiac portion of the right lower lobe, due chiefly to tumor (adenoma). Same case as Figure 3.

The adenoma of the bronchus and/or lung constitutes approximately 60 per cent of all benign tumors occurring in this area. Since about 80 to 90 per cent of the adenomas arise from the larger bronchi, this tumor will be seen via the bronchoscope much more frequently than the other tumors. As seen through the bronchoscope, the adenoma is a smooth mass projecting into the lumen of the bronchus, often round or lobulated, pinkish and containing many small vessels. The surface of the tumor bleeds easily on manipulation. These tumors usually have a broad base in the wall of the bronchus but they *may* be pedunculated. The other tumors as seen via the bronchoscope are similarly rounded projections into the lumen of the bronchus. They vary in size, color, vascularity and firmness, depending upon their composition. Biopsy of representative tissue is necessary before one can make a definitive histopathologic diagnosis.

THERAPY

The therapy for benign bronchopulmonary tumors is surgical and should conform to the specific needs of the case. Obviously, the patient whose condition does not permit removal of the tumor without inordinate risk should not be subjected to unwarranted surgery. Where surgery is performed, it is injudicious to sacrifice more lung tissue than is necessary to fulfill the specific requirements of the condition. At the same time, it is well to remember that the failure to eradicate completely the disease and its attendant irreversible complications may be equally inadequate. Treatment must be tempered with reason. The basic surgical modalities in the treatment of benign bronchopulmonary tumors are as follows:

Bronchoscopic Removal. In general, this method is inadequate in the treatment of such tumors, especially in cases of adenoma of the bronchus, since many extend through the bronchial wall and since many are potentially malignant. In spite of this, bronchoscopic removal has a definite place in the treatment of these tumors. The indications are (1) palliative therapy and (2) to permit evacuation of the contents of the lung distal to the obstructing tumor.

Bronchotomy. Local removal of the tumor by this means via transthoracic bronchotomy is indicated in those cases in which the tumor is confined to a local area in the bronchial wall. After the tumor is removed, the defect in the bronchial wall can be repaired by the method advocated by Gebauer.

Enucleation. In many instances the tumor is well encapsulated, movable within the substance of the lung, and close to the periphery of the lung, permitting complete removal with minimal sacrifice of pulmonary tissue. In such cases enucleation of the tumor is an ideal method of treatment.

Wedge Resection. A tumor which is reasonably movable within the lung tissue, fairly well circumscribed and somewhat deeper in the lung is best removed with the local pulmonary tissue. The method most suitable for such lesions is the wedge pulmonary resection which includes the tumor.

Segmental Resection. This procedure lends itself to the removal of local tumors within the depth of the lung and which are confined to one segment of the lung. It is also indicated in those cases in which the tumor arises within the segmental bronchus or comprises the segmental bronchus, leading to irreversible changes in the tissue distal to the obstruction.

Lobectomy. This method is indicated in those cases in which the tumor occupies a greater part of a lobe or there is considerable involvement of the lobar bronchus and/or there is irreversible damage to the pulmonary tissue distal to the tumor.

Pneumonectomy. The indications are similar to those of the lobectomy, except that the tumor is more proximally situated (in a main bronchus area) and/or the irreversible pulmonary tissue changes involve the greater part of the entire lung.

In all cases the least radical procedure should be utilized which accomplishes its purpose. While conservation of pulmonary tissue is desirable, it must not be at the expense of curative therapy. Regardless of which of the aforesaid methods is used, it must satisfy the dicta of sound surgical judgment in that (1) the tumor is removed completely, as shown in the frozen section studies made at the time of the operation, (2) the tumor is non-malignant, (3) the pulmonary tissue distal to the tumor which is irreversibly infected has also been removed, and (4) there has been no unnecessary sacrifice of pulmonary tissue. Although the frozen section may show the presence of a "benign adenoma" it is well to scrutinize the neighboring tissues and especially the lymph nodes for secondary involvement before the wound is closed, since these tumors are potentially malignant.

SUMMARY

1. A review of the subject of benign bronchopulmonary tumors and cases illustrative of some of these tumors have been presented.

2. The pitfalls in the clinical diagnosis of such tumors have been indicated and the surgical modalities in the management of such cases have been discussed.

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Hamartoma of the Lungs

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IN 1904 Albrecht[1] described instances of biliary hamartomas. He defined "hamartoma" as "tumor-like malformations in which occur only abnormal mixing of the normal components of the organ. The abnormality may take the form of change in quantity, arrangement, or degree of differentiation, or may comprise all three. The deduction to be drawn from the histologic examination of these formations is that they have originated in abnormal mixing of their development."

The lesions have been variously reported as papillomas, fibroadenomas, chondromas, mixed tumors, hamartoma chondromatosum, adenochondromas and lipochondromas. Many of these tumors embrace all of the bronchial anlagen, both mesodermal and endodermal tissues. Albrecht designated all of these mixed tumors as hamartomas. So-called chondromas of the lung are in reality hamartomas and, according to Jones,[2] they constitute 0.25 per cent of all routine autopsy cases. McDonald, Harrington and Clagett[3] report twenty hamartomas in a series of 7,972 necropsies, an incidence of 0.25 per cent. These "chondromas" of the lung contain bronchial epithelium in clefts between cartilaginous masses and may also include the mucoid, fibrous, lymphoid and muscular tissues. The term hamartoma should be reserved for this type of lesion.

Hickey and Simpson[4] reviewed forty cases of primary chondroma of the lung and added two cases of their own. Microscopic examinations of their own cases indicated a composition of islands of cartilage, myxomatous connective tissue, adipose tissue, mature fibrous connective tissue and papilliferous gland-like structures, covered by a single layer of non-ciliated cuboid or columnar epithelial cells. In some areas the tumors were covered by stratified ciliated epithelium and contained lime salt deposits. Generally the tumors contained the structures previously enumerated, although in a few instances osseous tissues were present.

Postlethwait et al.[5] report a hamartochondroma presenting itself endobronchially, thus causing bronchial occlusion. They reported thirteen such similar cases from their review of the literature.

Because pulmonary hemangiomas represent an alteration in quantity and arrangement of normally occurring structures of that particular organ, Simon[6] considers pulmonary hemangiomas to be hamartomas. They may produce polycythemia, clubbing of the fingers, cyanosis and variable degrees of dyspnea. Although these tumors conform to Albrecht's definition of hamartoma, hemangioma appears to be a more descriptive term. Hall[9] believed that many of the hemangiomatous lesions of the tongue, liver and spleen, as well as some fibromas of the kidney and rhabdomyomas of the heart, were hamartomas. Adenoma sebaceum, tuberous sclerosis, Lindau's disease, phacoma of the eye and neurofibromatosis have been considered by some investigators to be examples of hamartomas although this may be farfetched.

Verga[7] reported a tendency to invasion in one of his cases and listed several examples where metastases had apparently occurred. However, we share the opinion that pulmonary hamartoma is generally a benign lesion.

The usual pulmonary hamartoma measures several centimeters in diameter. It may, however, vary in size from less than 1 cm. in diameter to a very large proportion. Jones[2] described a case in which the hamartoma was so large that it occupied all of the right upper lobe of the lung. This is a very uncommon finding.

Sex, Age and Location. The incidence is generally considered higher in men in the proportion of 2 or 3 to 1. There is no significant age distribution. These tumors may be discovered at necropsy in older individuals, but with the advent of routine roentgenographic chest surveys it is anticipated that these lesions will be found more often in younger individuals.

Pulmonary hamartomas are said to be usually peripheral and generally just below the visceral pleural surface. However, they may occur anywhere in relation to the bronchial tree and pleural surface.

Signs and Symptoms. Secondary polycythemia, clubbing of the fingers, cyanosis and dyspnea may be expected if one would include pulmonary hemangiomas as hamartomas. However, hamartomas not producing bronchial obstruction frequently produce no abnormal symptoms or signs. Bronchial obstruction is rather a rare phenomenon in this condition. Usually the occurrence of the pulmonary hamartoma is first suspected on an incidental chest roentgenographic examination.

Roentgen Diagnosis. Pulmonary hamartoma is usually sharply circumscribed and well demarcated with no surrounding infiltrate. It is generally spheroid and may be lobulated. Calcification and sometimes ossification may be noted within the contour of the lesion. Hall[9] reported four cases of pulmonary hamartoma, all of which contained demonstrable calcium in the roentgenograms. Lemon and Good[8] showed evidence of calcification or ossification in eleven of seventeen cases. Calcification was noted in one of our three cases by roentgenography and ossification was seen in another case microscopically. Characteristically a hamartoma is indolent. It generally does not change in size or shape over a period of years. One of Hall's cases[9] was followed for five years and another for twenty-one years by repeated roentgenographic examinations with no demonstrable increase in size. The latter case showed an apparent increase in the amount of calcification while under observation. One of our own cases was followed for twelve years and showed probably a very slight increase in size (apparent growth of 0.5 cm. in one diameter) which we cannot completely account for on technical factors. In those instances in which a hamartoma (hamartochondroma) arises from the inner wall of the bronchus, there may be obstructive emphysema present initially to be followed by atelectasis and areas of obstructive pneumonitis.

Hall,[9] Hickey and Simpson,[4] and others have maintained that the roentgen appearance of a pulmonary hamartoma is sufficiently characteristic for an accurate diagnosis. This opinion is not shared by Lemon and Good[8] on the basis of their own experience, and we believe quite strongly that an accurate diagnosis without thoracotomy is impossible in most instances.

Most of the hamartomas are peripherally located and thus a bronchoscopic examination is usually of no value. Bronchography will simply indicate a tumor adjacent to one of the bronchial radicles. Laminographic roentgen studies may be of benefit in demonstrating the exact contour of the lesion and determining the presence of calcification or ossification. Thoracotomy with microscopy is the only definitive measure for establishing a diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is that of any of the solitary, spheroid, circumscribed pulmonary densities which may present themselves on the chest roentgenogram.

Peripheral Bronchogenic Carcinoma. This lesion at inception may very well simulate a hamartoma, but only exceptionally contains demonstrable calcification and generally grows rapidly in contradistinction to the known indolence of hamartoma. However, on rare occasions in a series of about 1,000 pulmonary malignant neoplasms, we have observed a small shadow that remained unchanged for two or three years and then suddenly acquired rapid growth. Occasionally there may be zones of breakdown within a carcinomatous mass which we have not observed or heard of in hamartoma. Metastases from peripheral bronchogenic carcinoma to the brain, bones, regional lymph nodes and other segments of the lung are very common early in the disease. It has been our experience that a lung lesion associated with cerebral symptoms is almost always a malignant neoplasm. Pulmonary hamartomas metastasize only very rarely, if at all. Hamartoma appears "built in." Malignant neoplasm resembles an "intruder," often causing changes in pulmonary dynamics such as atelectasis, raising of the diaphragmatic leaflet, mediastinal nodes, etc.

Tuberculoma. Tuberculoma may exactly simulate a hamartoma in appearance. Calcifications within the contour of tuberculoma are quite common (probably a good deal more so than in a hamartoma). Small, adjacent linear infiltrates or fibrotic strands may sometime be seen, while in a hamartoma the surrounding pulmonary tissues are normal. There may be other areas of involvement by tuberculous infiltrates both in the lungs and elsewhere in

the body. Areas of breakdown within the contour of tuberculoma may occur occasionally. Tuberculomas are less apt to grow perceptibly than bronchogenic carcinomas, but a demonstrable increase in size is not as rare as in hamartomas. It should be noted that on the basis of frequency of occurrence, when there is a differential diagnosis considered between tuberculoma and hamartoma, the former is the more likely diagnosis. In a tuberculoma some calcified regional lymph nodes may be present.

Chronic Lung Abscess. Occasionally a chronic lung abscess may assume a spheroid configuration with no demonstrable breakdown and thus simulate a hamartoma in appearance. Graham and Singer[10] have reported three cases of chronic lung abscess containing calcification. Usually, however, the cause of lung abscess is such that obvious roentgenographic evidence of breakdown occurs and the nature of the lesion becomes apparent. There may be "spill-over" into the dependent portion of the lungs.

Cyst. Pulmonary bronchogenous or enterogenous cysts may be filled with fluid and simulate hamartoma in that they appear circumscribed and spheroid. Here, again, progress films will indicate the true nature of the lesion, particularly when a bronchogenous communication is established or re-established and the fluid content of the cyst is drained. There may also be a change in the size and shape of a cystic lesion on roentgenograms taken in inspiration and expiration and during the physiologic maneuvers of Müller and Valsalva, while solid lesions such as hamartoma remain unchanged.

Infarct. Pulmonary infarcts are usually triangular in appearance shortly after their inception, although they may simulate ordinary zones of pneumonitis. About 40 to 50 per cent of infarctions are accompanied by pleural fluid. Hampton and Castleman[11] have demonstrated that occasionally multiple infarcts which are contiguous may present the appearance of a single solitary density simulating a hamartoma. However, the clinical history frequently suggests an infarct and the course in progress films is such that the diagnosis is generally not too difficult. The triangular or even the spheroid density which is caused by the infarct becomes smaller as weeks or months go by and residual linear densities simulating lobular areas of atelectasis are noted.

Arteriovenous Angiomatosis. There may be one or more lobulated irregular densities. These are usually connected by cord-like vascular densities. They may be frequently observed to pulsate roentgenoscopically. Angiocardiography is decisive.

Metastatic Pulmonary Carcinoma. A single solitary metastatic focus in the lungs may be confused with a hamartoma, but the course of the disease is such that these solitary densities grow rapidly in size and other opacities quickly appear. Frequently the presence of a known primary focus establishes a diagnosis immediately and there is no likelihood of confusion with a hamartoma.

However, one of Hickey's and Simpson's[4] patients had associated carcinoma of the stomach and another, carcinoma of the prostate. In their forty reviewed cases of hamartoma three had associated carcinomas elsewhere, namely, two in the prostate and one in a bronchus. Therefore when a pulmonary lesion is identified in the presence of a known malignancy elsewhere, careful consideration should be given in evaluating operability. One of our patients had an abdominoperineal resection with colostomy for carcinoma of the rectum in 1931 and is alive and well as of 1954, an interval of twenty-three years. He had associated pulmonary hamartoma which might have jeopardized the performance of a needed and life-saving surgical procedure. On August 19, 1954, he was discharged from this hospital in good condition following cholecystectomy for biliary lithiasis.

The differential diagnosis may be difficult, but with the advent of laminagraphy and other methods one is better able to evaluate the differential diagnosis. Biopsy, however, is the only basic, dependable and definitive diagnostic measure. As Miscall[13] expressed himself in a conference, "fortunately there is a relatively safe and simple method to establish a diagnosis." Therefore, a single solitary lesion of the chest in the presence of operable malignancy elsewhere should not deter the clinician from giving consideration to the possibility that it may not be metastatic and unrelated to primary disease. Benign conditions such as hamartoma, neurofibroma, cyst, tuberculoma, etc., may coexist in the presence of surgically curable primary malignant neoplastic disease. Not every nodulation is metastatic.

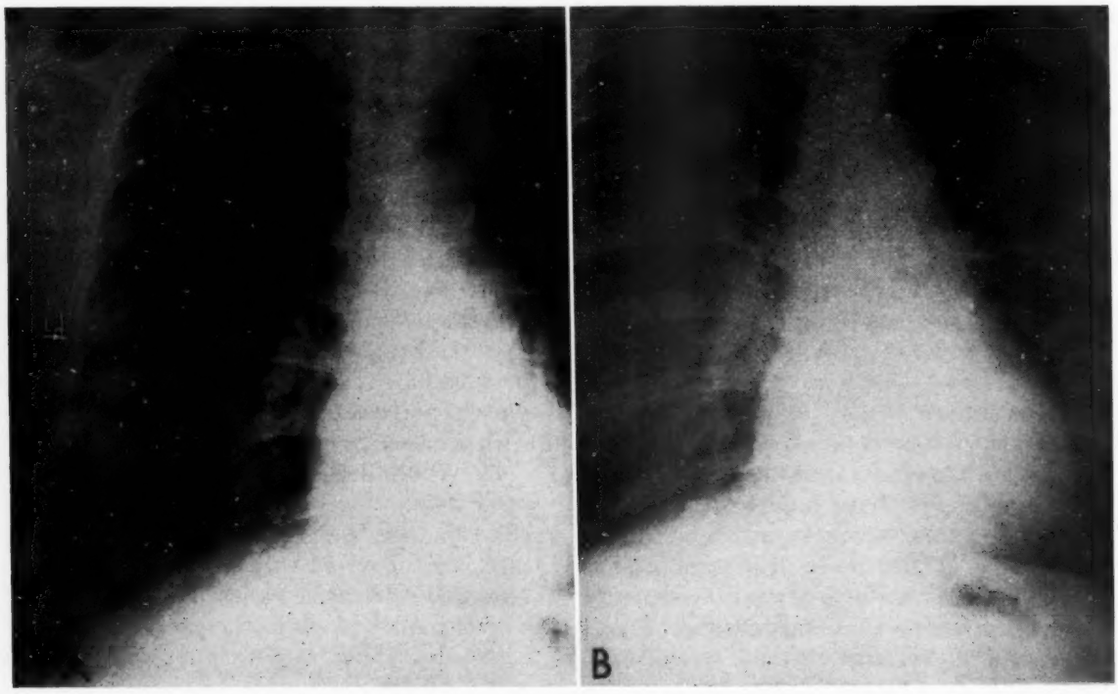

FIG. 1A and B. Case 1. A, chest roentgenogram January 17, 1949, demonstrates a mass in right mid-lung. Surrounding lung structures normal. B, chest roentgenogram November 2, 1949, identifying same mass with no increase in size.

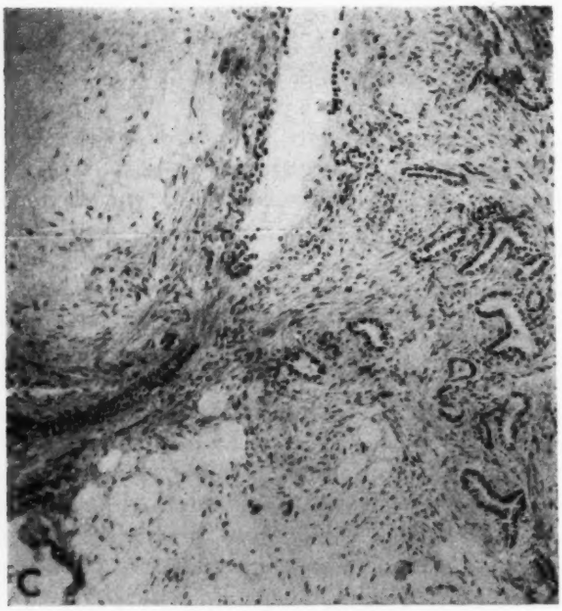

FIG. 1C. Case 1. Photomicrograph showing bizarre arrangement of bronchi; hematoxylin and eosin, × 100.

CASE REPORTS

CASE 1. This sixty year old white man was admitted to the hospital November 28, 1949, because of a right inguinal hernia of fifteen years' duration. A routine chest x-ray was diagnosed elsewhere as a nodule, "lobulated neoplastic disease." There was no significant respiratory history or any other symptoms. Physical findings outside of the hernia were essentially normal. The hernia became incarcerated and emergency herniorrhaphy was performed with an uneventful recovery.

The problem of the chest condition remained to be solved. Roentgenograms of the chest (Figs. 1A and B) showed a spheroidal, well circumscribed density in the right mid-lung which measured 2 by 2 cm. The lungs were otherwise clear. Laminagraphic studies showed no evidence of calcification in the lesion. The patient was transferred to the chest service and on December 30, 1949, a right-sided thoracotomy was performed. A solitary discrete tumor of the right lower lobe lying immediately adjacent to the interlobar fissure was found. The tumor was shelled out completely and a frozen section was reported as a benign tumor. The postoperative course was uneventful.

Pathologic report revealed the following: A gross specimen consisting of a circular mass measuring 2 by 2 cm. was sectioned. The external surface appeared to be fibrous capsule which was hemorrhagic and on section showed

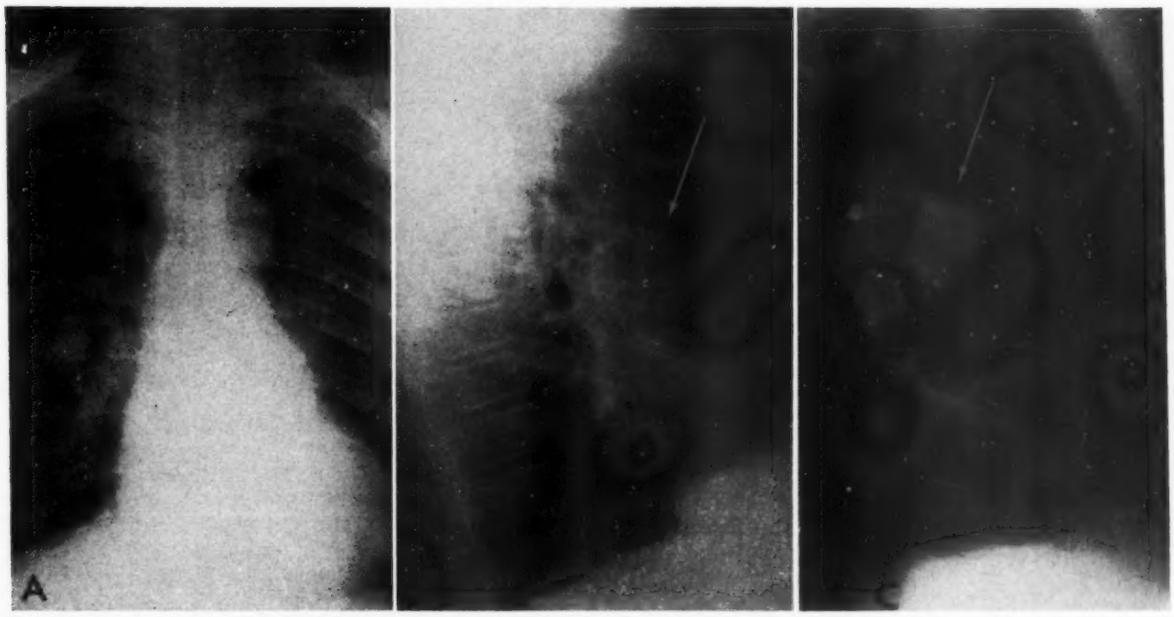

FIG. 2A to C. Case II. A, chest roentgenogram March 19, 1951, showing mass in the right lung. Surrounding lung structure clear. B, lateral projection. C, lateral laminagram with arrow pointing to mass showing punctate calcification.

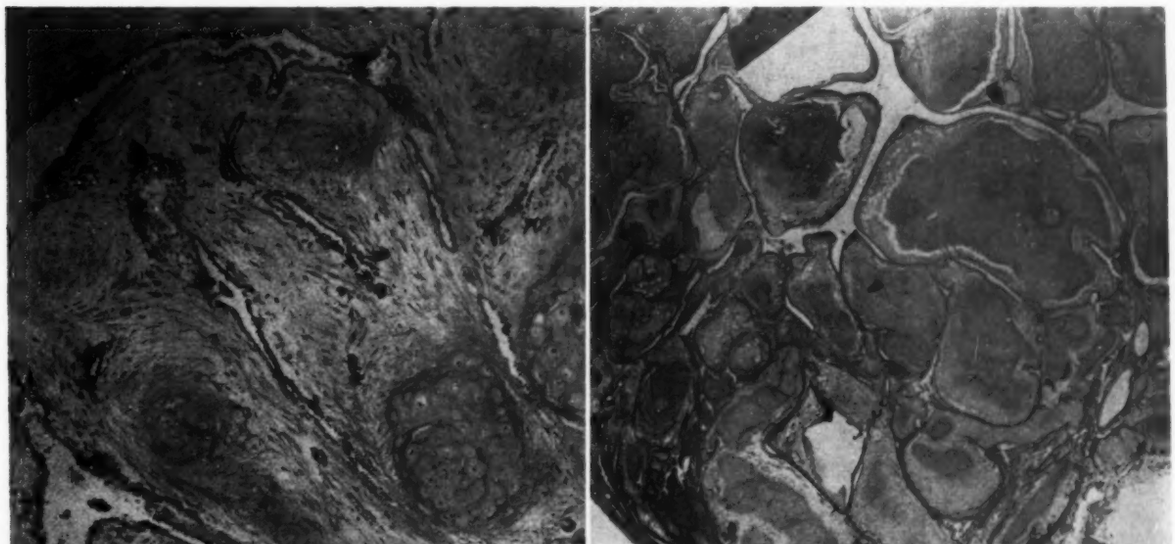

FIG. 2D and E. Case II. D, photomicrograph showing bronchial hamartoma; hematoxylin and eosin, × 20. E, photomicrograph and higher magnification showing benign epithelium and atypical cartilage in hamartoma; hematoxylin and eosin, × 100.

mucoid, firm cartilaginous tissue and a few whitish areas. Microscopic examination showed nodules of cartilage with intervening connective tissue and fat enclosing narrow spaces lined by single-layered, cuboid, non-ciliated epithelium. (Fig. 1C.) The microscopic diagnosis was pulmonary hamartoma (benign).

CASE II. This fifty-three year old Negro man was admitted March 16, 1951, with a story of a mass in the right lung discovered in a routine chest examination upon coming to the hospital. The patient complained of a cough of about ten years' duration which was productive of about 2 tablespoons of dark,

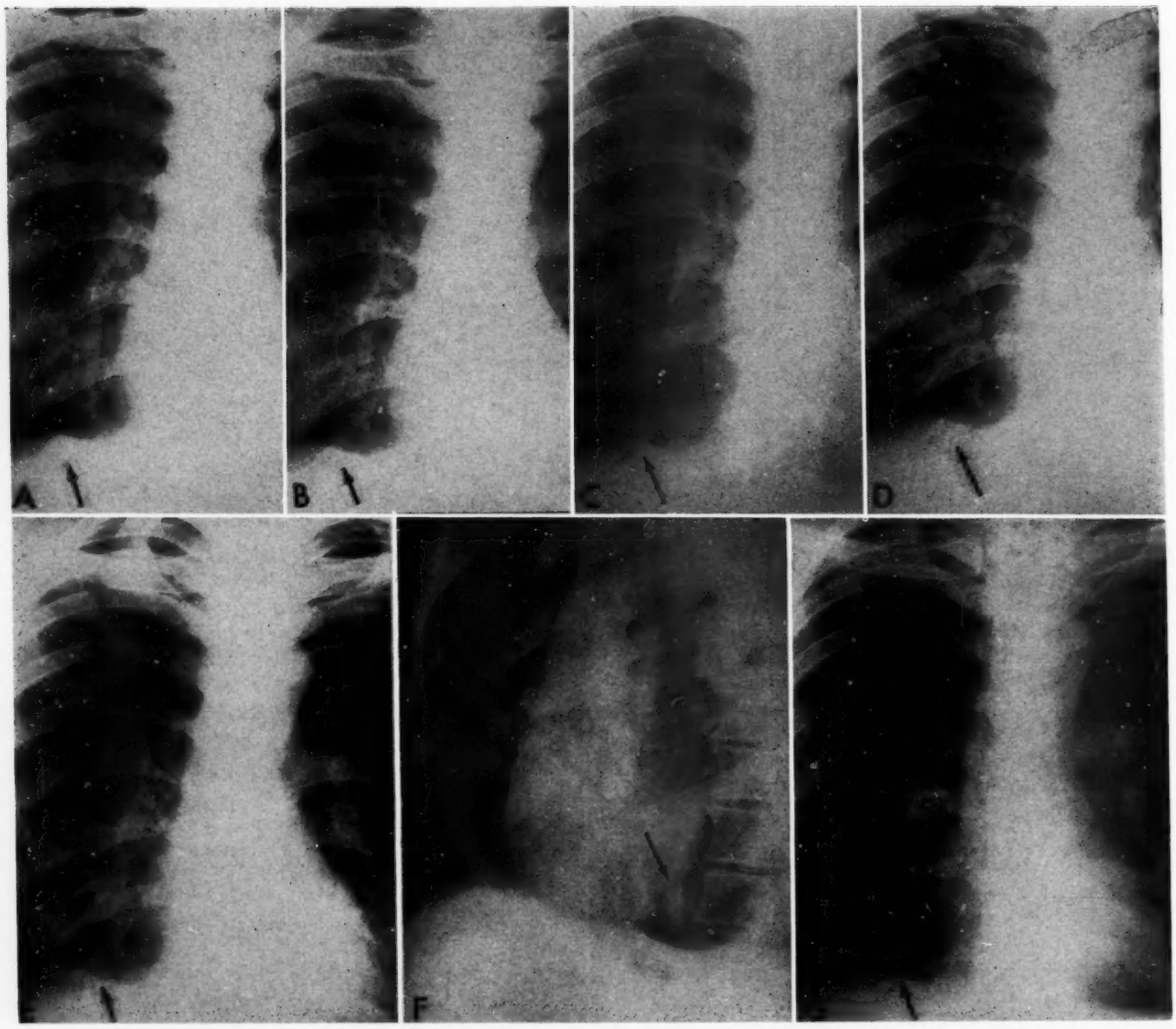

FIG. 3. Case 11. Radiographically recorded, surgically and microscopically authenticated case of hamartoma of twelve years' progression. A, chest January 2, 1937, shows small mass at the base of the right lung. Arrow points to mass which is mostly concealed by overlying diaphragmatic leaflet. Mass measures 2 by 1.5 cm. B, roentgenogram dated March 11, 1940. Diaphragmatic leaflets slightly lower than in A. Half of the mass is clearly visible above the diaphragm and the other half is somewhat obscured. Density measures 2 by 2 cm., a probable growth of 0.5 in three years. C, chest on March 15, 1944, demonstrates that most of the mass is above the level of the diaphragmatic leaflet. No increase in size over the roentgenogram made in 1940. D, chest roentgenogram, January 26, 1945, again shows lesion partially below the diaphragmatic level (arrow). E, chest roentgenogram dated February 23, 1949, again demonstrates a mass (arrow). F, left posteroanterior oblique projection (arrow pointing to mass which is very clearly visualized). G, posteroanterior chest roentgenogram, March 7, 1949, showing most of the mass above the diaphragmatic level (arrow). It measures 2 by 2 cm. and no increase in growth over exposure made in 1940 (C).

mucoid, non-foul sputum daily with no history of hemoptysis. There were no other significant symptoms.

Pertinent abnormal physical findings were mild hypertension, central opacities in the eyes, slight left heart enlargement and a Grade 11 systolic murmur at the base of the heart. There was also atrophy of the left testicle and questionable enlargement of the prostate.

Chest roentgenographic studies (Fig. 2A and B) showed a spheroid density in the right mid-lung measuring 2.5 by 3.0 cm. Laminagraphic studies (Fig. 2C) showed punctate calcifications within the contour of the mass. Further studies including barium enema, gastrointestinal series, intravenous urography, hemogram, urine analysis, sedimentation rate and blood chemical studies were all within

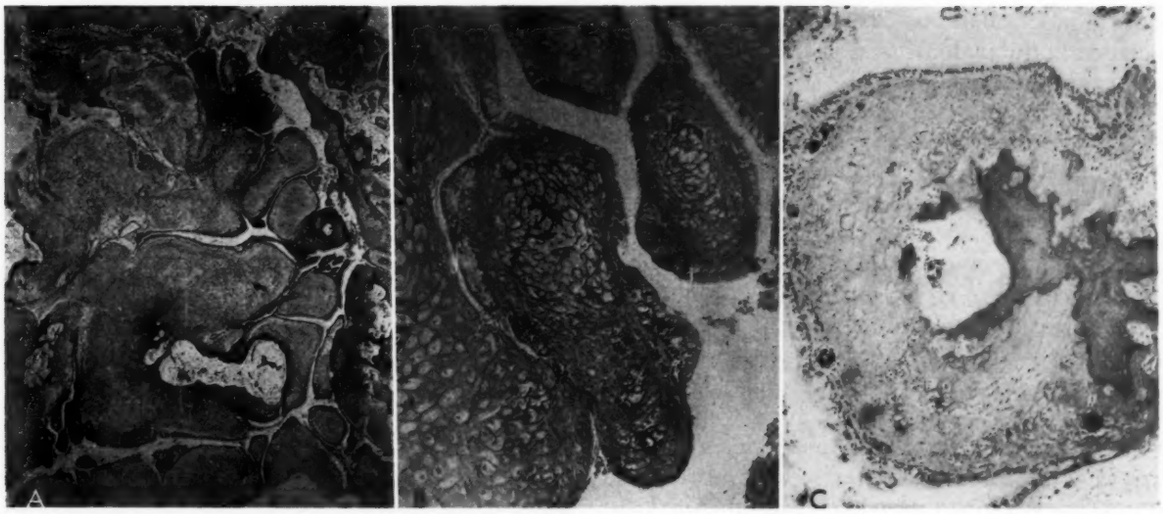

FIG. 4. Case III. A, photomicrograph showing typical features of bronchial hamartoma; hematoxylin and eosin, × 20. B, photomicrograph, higher magnification, illustrating benign ciliated bronchial epithelium and atypical bronchial cartilage; hematoxylin and eosin, × 100. C, photomicrograph demonstrating metaplastic ossification and atypical cartilage; hematoxylin and eosin, × 100.

normal limits. Papanicolaou-prepared sputum from bronchoscopy showed no neoplastic cells. The P. P. D. tuberculin test in the first strength was positive, with a 2 plus reaction to forty-eight hours.

Thoracotomy was performed May 11, 1951, and a mass described in the roentgenogram was found attached to a very small bronchus. It measured 3 cm. in diameter and was located in the area of the fissure between the upper and middle lobes. The fissure itself was rudimentary and whether this mass was in the upper or middle lobe could not be clearly determined. The mass was firm, oval and shelled out easily. The postoperative course was uneventful.

On gross examination the specimen consisted of a firm nodule measuring 2.5 by 2 cm. On section the mass was seen to be composed of a central, dense, homogeneous, grayish-white tissue from which many large nodules radiated toward the circumference. Microscopically, there was a multilobed sheet of atypical cartilage with connective tissue, fat and clefts between the lobes lined by epithelium of bronchial type. (Fig. 3D and E.) The microscopic diagnosis was epitheliochondromatous hamartoma.

CASE III. This forty-eight year old white man was admitted to the hospital February 18, 1949, for evaluation of a previously demonstrated chest lesion seen on roentgenographic study in 1948. The patient had had an abdominoperineal resection with colostomy for carcinoma of the rectum in 1931. During the usual follow-up studies in 1948 a chest roentgenogram showed a small rounded nodule in the right lower lung posteriorly. Review of a chest roentgenogram made in 1937 (Fig. 3A) showed the nodule to be present at that time, measuring 2 by 1.5 cm. It measured 2 by 2 cm. on the chest roentgenogram taken in 1949 (Fig. 3G), suggestive of a 0.5 cm. increase in size in one of the diameters in twelve years.

During the month previous to admission the patient had had a dull pain in the right side of the chest which was rather constant and radiated to shoulder, head and neck. The patient complained of a chronic cough with expectoration of a small amount of whitish mucoid sputum daily without blood or foul odor. The remaining history was not relevant.

Examination revealed a middle aged patient not seriously ill. The pertinent abnormal physical findings consisted of a functioning left-sided colostomy, a few moist rales in the right base, bilateral inguinal hernias and a moderate prostatic enlargement.

Laboratory data revealed the following: Hemogram, urinalysis and spinal fluid examinations were normal. There were no acid-fast bacilli in the sputum. Glucose test showed a mild diabetic curve. Roentgenographic studies of the gastrointestinal, urinary and skeletal systems disclosed no abnormalities except for the functioning colostomy, and the chest

roentgenograms showed a spheroidal, circumscribed nodular density in the base of the right lung measuring 2 by 2 cm.

On March 28, 1949, right-sided thoracotomy was performed. A small circumscribed tumor was found in the right lower lobe and lobectomy was performed. The patient made an uneventful recovery.

Pathologic report revealed that the specimen consisted of the right lower lobe of the lung. Three centimeters from the edge of the lobe there was a rounded calcified tumor measuring 2.5 by 2.5 cm. On section this mass showed a calcific surface, underlying which was a firm, white, grumous material. Microscopically (Fig. 4A, B and C) the mass consisted of a bronchial type. Some of the cartilage was atypical. In places there was connective tissue between the epithelium and the cartilage. A few areas of cartilage were ossified. (Fig. 4C.) The microscopic diagnosis was pulmonary hamartoma.

This patient had carcinoma of the rectum associated with a benign hamartoma. Through surgery the patient was apparently cured of carcinoma of the rectum; and had the nodule been identified prior to the time of surgery, the patient might have been considered inoperable. Identification after surgery might lead one to believe that metastatic disease occurs postoperatively. This patient is alive in 1954, twenty-three years following surgical resection of carcinoma of the rectum.

SUMMARY AND CONCLUSIONS

Three cases of pulmonary hamartoma observed at this hospital are presented. In one patient there was associated carcinoma of the rectum and it is indicated that not all nodular densities in the lung associated with neoplastic disease represent metastases.

1. The incidence, definition, and gross and microscopic anatomy of pulmonary hamartoma are presented.

2. The common locations of hamartoma in the lung are described.

3. The clinical signs and symptoms of pulmonary hamartoma are listed.

4. There are no pathognomonic roentgen signs of pulmonary hamartoma. It may be suspected in a single solitary spheroidal opacity in the lung of long duration without appreciable growth.

5. Three personally observed cases of pulmonary hamartoma are presented, including a summary of the history, physical findings, roentgen appearance and pathologic reports.

6. Hickey and Simpson's two personally observed cases had associated malignant neoplasms. Three of their forty reviewed cases in literature and one of our own three cases had associated primary neoplastic malignant disease giving an incidence of six of forty-five cases.

7. Not all nodular lesions in the chest with diagnosed primary carcinoma elsewhere represent metastatic disease.

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Lung Cancer and Smoking

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The marked increase in frequency of lung cancer throughout the world has stimulated numerous investigations in order to attempt to determine the possible causes of this disease. The conclusion drawn at the International Conference on Lung Cancer in 1952[1] was that a significant and absolute increase had taken place; and a great deal of statistical evidence has been accumulated to demonstrate an association between the rise in the incidence of lung cancer and tobacco smoking, with a resultant controversy as to the merits of the data.

The Minister of Health in England[2] recently stated that there is a strong presumption of causal relationship of smoking to carcinoma of the lung and advised that the State support organized attempts to clarify the situation. The majority of reports on the subject, particularly those from England, emphasize the high incidence of proved carcinoma of the lung in heavy smokers of long duration. However, certain authorities believe that such conclusions between the incidence of cancer of the lung and tobacco smoking is fortuitous; that adequate control study has not been carried out; and that the experimental production in animals of skin neoplasm with cigarette tars bears little relationship to the problem in human beings.

Other factors cited for the increase in the incidence of cancer of the lung are better diagnostic facilities, a decrease in the number of deaths from infectious diseases and the increased life span of the general population. Heuper[15] has pointed out that the predominance of cancer of the lung has increased in men and has remained stationary in women, while at the same time there has been an increasing equalization of the intensity of exposure of both sexes to cigarette smoking.

Table 1

STATISTICS OF DEATHS DUE TO CANCER OF THE RESPIRATORY TRACT IN THE LAST FIFTY YEARS*

Year	No. of Deaths								
	England	U. S. A.	Germany	France	Italy	Norway	Switzerland	Scotland	Canada
1901	651	3,807	3,958	3,316	886	42	100	72	241
1949	12,395	19,518	6,164	5,554	3,907	203	700	1,325	1,436

* From the Report of the World Health Organization, Geneva, 1952.

A study of large autopsy series has in most cases shown a marked increase in the incidence of primary lung cancer. In only one recent autopsy series in England[10] did the incidence of lung carcinoma reveal no increase. In all other reported series in England[10] the rise from 1900 to 1925 was twofold and from 1925 to 1950 about fourteenfold, and by 1950 lung cancer was the most important neoplasm recorded. Of all the carcinoma deaths in men, 24 per cent were due to cancer of the lung (in age group forty-five to fifty-nine). Table 1 illustrates the increase in deaths from carcinoma of the respiratory tract reported during the last fifty years in different nations.[4]

According to Doll[10] isolated autopsy series in India and Africa have shown the incidence of lung cancer to be very low, but it is not accurately known whether the smoking or chewing of tobacco is more common in these particular areas.

The following reasons have been offered to explain the increasing incidence of lung cancer:[8,9]

(1) increase in recorded death rates has occurred in all countries; (2) the disease is a common clinical entity at the present time; (3) in university hospitals in which the autopsy rate is over 90 per cent lung cancer has shown a real increase; (4) the increase is greater in men than women; (5) age distribution of lung cancer in man is different from that of all other major types of cancer in man; (6) mortality from this disease is the same among doctors as among the rest of the population.

Included in the reasons proposed to explain the increase in the incidence of carcinoma of the lung have been atmospheric pollution, occupational hazards, exhaust fumes of vehicles and, most important of all, tobacco smoking. A minority have also considered the role of the pandemic influenza of 1918 which may have brought about some changes in the respiratory epithelium of some patients.

Among the exposures which have been associated with the pathogenesis of carcinoma of the lung are the following occupational hazards:

1. *Saxonia uranium ores:* Miners in the Schneesberg mines in Saxonia and in the Joachmista mines in Bohemia have died from cancer of the lung in large numbers.

2. *Chromate industries:* The German literature contains many reports of a high incidence of lung cancer in this occupation. In England, in a study of 724 workmen by Bidstrup[5] only one case of cancer of the lung was found while Imprescia[16] surveyed 400 workmen in the chromate industry and found seven patients with this disease.

3. *Asbestos industries:* In England, in a group of 235 patients with asbestosis thirty-one cases of cancer of the lung were found, but it is believed that with the present safety ventilation system the hazard is greatly reduced.[27]

Doll and Hill[8] have shown that there is a close association between urban residence and the incidence of the disease, but the possibility that townsmen smoke more than rural dwellers would seem to be insufficient to account for the disparity.

All the recent evidence presented by numerous authors seems to incriminate tobacco smoke as the vehicle conveying an agent responsible for a large proportion of the cases of lung cancer, and intensive research is being carried out in an effort to isolate the carcinogen in tobacco so that it may be eliminated and smoking made less hazardous. As pointed out by Ochsner[23] the per capita consumption of cigarettes in the United States doubled during the decade 1920 to 1930, and eighteen years later, 1938 to 1948, the incidence of lung cancer increased from 4.2 to 11.3 per cent. This increase in tobacco consumption is reflected twenty years later by a significant increase in the incidence of lung cancer and he believes that bronchogenic carcinoma will become more frequent than any other neoplasm and that by 1970 it will cause 18 per cent of all cancer deaths. Although difficult to prove scientifically the evidence points to tobacco smoking as a possible etiologic agent.

This increase in lung cancer is real[2,17,29] and in relation to this it is significant that in the year 1948 at Memorial Hospital[30] there were twice as many admissions for cancer of the lung as for cancer of the stomach. There has also been a sharp increase in the ratio of males to females. In 1910 the ratio was 3:1 while in more recent reports it has been found to be as high as 24:1,[21] the median being about 8:1.

Evidence to show the carcinogenic potentialities of tar and arsenic in tobacco has been accumulating rapidly.[20,23] A recent survey of the content of arsenic of various cigarettes smoked in North America and Europe showed that no direct correlation existed between lung cancer and the amounts of arsenic. Although American cigarettes were found to have a greater arsenic content than Turkish cigarettes, an autopsy series in Istanbul, where Turkish tobacco is smoked exclusively, showed an equally high increase of cancer of the lung. Approximately 15 mg. of arsenic have been found in a pound of tobacco[25] and the amount of tar taken into the lungs during a long period of heavy cigarette smoking is remarkable, being estimated at about 0.8 quarts per year.[28,32]

As far as the experimental production of pulmonary tumors in animals is concerned, little can be drawn from the evidence presented. Most investigators have attempted to demonstrate carcinogenic properties of tobacco tars in small animals like mice or rabbits. While some observers have noted that the application of carcinogenic agents to the skin of these animals resulted in the production of skin cancers, the common pulmonary tumor of mice is the papillary adenocarcinoma which seems to be of alveolar origin and very dissimilar to the

human type of neoplasm. Roffo[25] in Buenos Aires in 1937 produced cutaneous papillomas in rabbits' ears by the application of products of distillation of tobacco smoke and attempted to isolate the particular carcinogenic agent. Benzopyrene was also found in the distillation products of tobacco and this is a well known carcinogenic agent. According to Doll[10] tumors more like the human type have been produced in mice by the insertion of cotton threads impregnated with 1-, 2-, 5-, 6-dibenzathracene directly into the lungs and also by implantation of lung tissue from embryos of mice along with a solution containing methylcholanthrene or dibenzanthracene into the thigh muscles of adult animals and finally by the administration of radioactive cerium in the form of an aerosol. Essenberg[12] using a strain of mice with a high incidence of spontaneous pulmonary tumors produced an increased incidence in this strain of tumors by exposure to a high concentration of cigarette smoke. Recently Wynder et al.[34] were able to produce epidermoid carcinomas in the skin of mice by the application of condensed cigarette tar. At the end of two years in 44 per cent of the eighty-one mice painted with condensed cigarette tar cancer of the skin developed, whereas in none of the control animals painted with acetone alone did any cancer develop. These animal data have proved that tobacco tar contains carcinogenic elements of a specific nature and that the chronic irritation due to the smoke, *per se*, is not carcinogenic. Other irritants can be found in the paper used to wrap cigarettes, insecticide spray used on tobacco plants and other aromatic ingredients used in preparation of tobacco.

Many believe that the most dangerous element in tobacco smoke is nicotine. A man who smokes forty cigarettes daily, at a rate of one cigarette per ten minutes (approximately six hours a day, forty-two hours a week) inhales a good deal of nicotine because one cigarette is equivalent to 1 mg. of nicotine. Of the nicotine that enters the mouth, half is ejected immediately if the man does not inhale. However, the average inhaler absorbs nearly all the nicotine into the respiratory tract and blood, and eliminates it slowly in the urine. The action of nicotine is accepted as dangerous to the vascular system but it is not known whether it is carcinogenic. It is believed that the currently used filters for cigarettes are effective only in eliminating some of the tars of the tobacco, but not a considerable amount of nicotine.

Many attempts have been made to measure quantitatively the role of exposure to tobacco fumes in the production of lung tumors. For example it has been estimated that the smoking of sixty cigarettes a day with inhalation result in the intake of 400 gm. of tar a year.[32] However, the action of tobacco must differ because of the modes of use, namely, if it was smoked or chewed. Some observers are of the opinion that smoking is more dangerous in periods of stress and that inhaling is a definite factor in determining severity and chronicity of exposure. It has been repeatedly pointed out that it is rare to find cancer of the lung in a man who has not been a heavy smoker for many years.[19,21,30,32] In Iceland Dungal[11] reports the consumption of tobacco in 1945 to be at the same level per capita of population as the consumption was in England in 1920, and an autopsy series in Iceland revealed cancer of the lung to be uncommon at that time. In the United States Wynder and Graham[33] reported a very small percentage of non-smokers in a large group of male patients with this neoplasm and ten times as many non-smokers in a controlled hospital group. It was pointed out that frequently a lag period of one to two decades was noted between cessation of smoking and the appearance of this tumor, but over 96 per cent of the patients with lung cancer had smoked for over twenty years. Graham[13] emphasized the rise to be only in squamous carcinoma and not adenocarcinoma, which was found to be equally distributed between the two sexes and that only the increase in epidermoid carcinoma was directly related to tobacco smoking.

Doll and Hill[8] studied a group of patients with cancer of the lung and an equal number of matched controls in various English urban and rural hospitals and found only 10.5 per cent non-smokers in 1,357 males with carcinoma of the lung, while there were 4.5 per cent non-smokers in the controls. Another English report[22] of 100 patients with proved cancer of the lung found over one-third of the patients had smoked more than twelve cigarettes daily while only one-fifth of the controls smoked as much. Attempts to correlate occupational factors, exposure to atmospheric pollution or inhalation of tobacco smoke were inconclusive in this series.

Among the more recent clinical reports is one by Rigdon and Kirschoff.[24] A higher percentage of patients who did not have cancer of the lung smoked less than fifteen cigarettes a day, while among patients with cancer of the lung a higher percentage smoked more than fifteen cigarettes a day.

Sadowsky[26] in reviewing the smoking history of 3,081 patients with cancer of the lip, tongue, oral cavity, esophagus, pharynx and larynx found that the rate of cancer of the lung in the smoker group was five times that of a non-smoker group. However, no increase was observed in the incidence of cancer of the larynx following the increase in cigarette consumption and it would therefore appear that there is less effect of tobacco on laryngeal than alveolar epithelium. A survey conducted in Finland[18] in 1953 showed that there were 99 per cent smokers in a group of 336 men with proved cancer of the lung while in the control group only 82 per cent were smokers. The striking feature of this report was the large number of boys that began smoking at the early age of ten or so. The majority of their patients had smoked for from three to four decades. As in all other series the incidence in women was low and no difference was found in environmental factors. A survey of the problem in California[6] has shown that there are more deaths from cancer of the lung than pulmonary tuberculosis and that in men aged forty-five to sixty-four it accounts for 4 per cent of all deaths. In a review of 518 proved cases they found 472 epidermoid and forty-six adenocarcinomas. Of the patients with lung cancer 93 per cent were smokers as compared with 76 per cent of the controls. The increased frequency of lung cancer was noted when tobacco was used in the form of cigarettes. No such increased frequency was noted when tobacco was used in pipes, cigars or for chewing. In fact 68 per cent of the control group used tobacco in a form other than cigarettes exclusively, against 15 per cent of the lung cancer patients.

Since the annual prevalence of cancer of the lung in men aged forty to forty-nine is 15.5 per cent/100,000, Cornfield[7] devised a formula to estimate the prevalence rates of lung cancer per 100,000 men in smokers as compared with non-smokers and the estimated rates of cancer of the lung per 100,000 males of selected ages and various cigarette habits. Breslow[6] in using this method presented a table (Table 11) of the estimated prevalence rate of lung cancer per 100,000 men calculated from various reports in the literature. According to this formula in our series the prevalence rate of lung cancer in male smokers of all ages is five and a half times as great as for non-smokers.

TABLE 11

ESTIMATED PREVALENCE RATES OF LUNG CANCER PER 100,000 MALES OF SELECTED AGES AND VARIOUS SMOKING HISTORIES

Authors	No. of Cases		Relative Prevalence Rates	
	Lung Cancer	Control	Heavy Smoking	All Quantities
Patients aged 50–59				
Doll and Hill	276	275	13	6
Wynder and Graham	258	210	27	11
Sadowsky et al	198	208	7	4
Breslow et al	213	213	17	7
Patients aged 60–69				
Doll and Hill	197	199	..	..
Wynder and Graham	187	170	29	15
Sadowsky et al	76	71	9	4
Breslow et al	168	169	25	5

From Table 11 it becomes evident that cigarette smokers run from four to fifteen times the risk of developing lung cancer and the relative prevalence in heavy smokers is estimated at seven to twenty-nine times that for non-smokers.

Levin[20] in a review of the figures from the Roswell Park Memorial Institute indicates that the risk of developing lung cancer is at least six times greater in cigarette smokers than in non-smokers. He reports the risks among pipe and cigar smokers to be much less and found that among men aged thirty years and over who are light smokers the risk is about doubled and in those smoking twenty cigarettes daily, ten times as great as in non-smokers. It becomes apparent that not only the irritant itself is important, but also the chronicity of exposure is significant.

No one knows of any single specific cause; but if one assumes a number of additive factors working together over a period of years, then the evidence to be presented supports the theory that chronic heavy smoking is one of the responsible factors in a high percentage of all cases of lung cancer.

MATERIAL AND METHODS

In our series of 2,000 cases of lung cancer, many of the earlier records are incomplete regarding the patients' smoking histories and not suitable for this statistical survey. With the financial aid and medical advice of the American Cancer Society, we undertook a study of the relation of smoking to the incidence of cancer of the lung in the following fashion. A trained interviewer was coached by a psychologist and given full responsibility for the interviewing of every patient coming to the Thoracic Clinic at Memorial Hospital regardless of his complaints or the nature of his disease. From 1950 to 1952 a series of 769 consecutive patients was studied and of this group, 301 were proved to have cancer of the lung. The remaining group was used as a control. So we have, as the basis for study, a large group of patients all in the cancer-of-the-lung age group, all with some problem related to the chest, and all seen in one clinic and interviewed by an unbiased, trained observer. When enough time had elapsed to allow for definite histologic diagnoses of the disease, we then separated the true cases of cancer of the lung and used the remaining group as a control.

Diagnosis. A positive histologic diagnosis of cancer of the lung was established by one or a combination of the following methods: (1) sputum smears; (2) bronchoscopy and biopsy; (3) bronchoscopy and cytologic washings; (4) aspiration biopsy; and (5) exploratory thoracotomy and open biopsy.

Formula. The formula setup for evaluation of smoking habits of the patients is as follows: class 0: non-smoker; class 1: minimal smoker (less than twenty cigarettes a day); class II: moderate smoker (up to twenty cigarettes per day for twenty years or more); class III: heavy smoker (twenty to sixty cigarettes per day for twenty or more years with inhalation). (One pipe equals two and a half cigarettes; one cigar equals five cigarettes.)

DATA

There were 301 patients with histologically proved cancer of the lung, 265 men and thirty-six women. In the control group there were 468 patients of whom 287 were men and 181 women. The number, sex and average age of both patients with cancer of the lung and control patients are shown in Table III and diagnoses in the control group in Table IV. All the diagnoses in the 301 patients with cancer of the lung were made by means of positive histology and/or cytology. (Table V.)

Male Patients with Cancer of the Lung. In studying the 265 male patients with histologically proved cancer of the lung we found that 260 were smokers and five non-smokers. In the male control group 250 were smokers and twenty-seven non-smokers. As seen in Table VI, 98.2 per cent of the cancer group were smokers and 1.8 per cent non-smokers.

TABLE III
COMPARISON OF CONTROL GROUP WITH CANCER OF LUNG GROUP

Sex	Cancer of Lung		Control	
	No.	Average Age (yr.)	No.	Average Age (yr.)
Male.....	265	59.1	287	54.2
Female.....	36	55.8	181	51.6
Total.....	301	58.6	468	52.9

In comparing these figures with the previous report from this hospital and those published in England by Doll and Hill, one can see that our latest results correspond rather closely with the English figures for the group with lung cancer, but we did find a larger percentage of non-smokers in our control group.

In classifying smoking habits we divided the patients according to whether or not they deliberately inhaled the tobacco smoke. This was not feasible, however, because patients interpreted the question differently and most cigar smokers did not intentionally inhale. It seemed logical, then, to divide all patients into three groups, classified as minimal, moderate or heavy smokers. Table VII shows that of all the male patients with cancer of the lung who smoked, 73 per cent were heavy smokers, while 24 per cent were moderate and 3 per cent minimal. These figures do not differ markedly from the previous report except for an increase in the heavy-smoker group.

The nationality and age of male patients with cancer of the lung are shown in Table VIII. The youngest male patient was thirty-seven years old and the oldest eighty-four. The average age at which they began to smoke was

nineteen years and there was one patient who started at the age of three.

In reviewing the nationality of the male patients, about half were born in the United States and the remainder were from European countries. Only two patients came from Turkey, but since all patients lived in the United States it is assumed that they all smoked the American type of cigarette, which has a rich arsenic content. Neither racial nor national background seemed to exert any definite influence.

It is evident that 90.3 per cent of the control group were smokers as compared with 98.2 per

TABLE IV

DIFFERENT DIAGNOSES IN CONTROL GROUP OF 468 PATIENTS WITHOUT CANCER OF LUNG

Site	No.	Site	No.
Head and neck		Stomach	
Cancer of nasopharynx	1	Cancer	2
Adenoma of tongue	3	Colon	
Cancer of alveolar ridge	2	Cancer of sigmoid	1
Cancer of floor of mouth	3	Cancer of rectum	1
Cancer of thyroid	2	Liver	
Adenoma of thyroid	7	Cancer of hepatic ducts	1
Cancer of maxillary antrum	3		
Total	21	Total	92
Larynx, trachea, lungs		Mediastinum	
Cancer of intrinsic larynx	2	Mediastinal tumors	11
Trachiectasis	1	Schwannoma	5
Extrinsic larynx tumor	4	Pericardial cyst	3
Metastatic tumor	10	Neurosarcoma	1
Emphysema	9	Hemangioma	1
Bronchial adenoma	5	Aneurysm	4
Bronchitis	7	Chondrosarcoma	2
Bronchiectasis	13	Osteogenic sarcoma	1
Pneumonitis	17	Teratoma	2
Pulmonary tuberculosis	31	Hygroma	1
Pleural calcification	2	Hodgkin's disease	7
Lung abscess	10	Reticulum cell sarcoma	2
Anthracosis	1	Lymphosarcoma	2
Lung cyst	11	Diaphragmatic hernia	5
Pulmonary adenomatosis	1	Hiatus hernia	5
Metastatic tumor, primary unknown	7	Rhabdomyosarcoma	1
Pleurisy	2	Thymoma	4
Atelectasis	2	Total	57
Chronic lung disease	1	Breast	
Mesothelioma	1	Cancer	33
Hamartoma	1	Genital Tract	
Boeck's sarcoid	4	Ovarian cancer	1
Total	142	Cancer of cervix	3
Gastrointestinal tract		Cancer of uterus	2
Esophagus		Total	6
Achlasia	16	Genitourinary Tract	
Cancer	53	Cancer of testis	2
Leiomyoma	1	Cancer of bladder	1
Stricture	2	Cancer of kidney	4
Abscess	1	Total	7
Congenital, short esophagus	2	Myocardial disease	1
Diverticulum	12	Undiagnosed	47
		No disease found	62
		Total, all cases	468

cent of those patients with cancer.[31] There is a statistically significant difference in the number of non-smoker control males (9.7 per cent) as compared with the number of non-smoker males with cancer of the lung (1.8 per cent). Furthermore, there is a much higher proportion of heavy (class III) smokers in the male lung cancer group (73 per cent) as compared with that in the control male group (57 per cent). This, coupled with the very high incidence of smokers in the lung cancer group, gives strong support to the argument that smoking must play a significant role in the background of patients in whom bronchogenic carcinoma develop. However, the widespread use of tobacco throughout the world makes it very difficult to find a very large number of control patients who have not smoked more than twenty years.

TABLE V
METHODS OF DIAGNOSIS USED

Method	Male	Female
SV*	37	4
P and SV	71	12
P†	157	20
Total	265	36

* SV indicates diagnosis with positive Papanicolaou smear

† P represents diagnosis by a positive biopsy as obtained by the various technics discussed

TABLE VI
SMOKING HABITS OF MALE PATIENTS WITH LUNG CANCER

Reference	Percentage of Smokers		Percentage of Non-smokers	
	Lung Cancer	Control	Lung Cancer	Control
Present series	98.11	90.3	1.89	9.7
Watson	95	89	5	11
Doll and Hill	99	95	0.5	4.5

TABLE VII
MALE PATIENTS WITH CANCER OF THE LUNG

Smoking Habit	Inhalers	Non-inhalers	Total (average %)
Minimal	1	6	3
Moderate	50	13	24
Heavy	172	18	73
Total	223	37	

TABLE VIII
AGE AND NATIONALITY OF MEN WITH CANCER OF THE LUNG

Cancer of Lung	No. of Cases	Per cent	Age		
			Oldest	Youngest	Average at Start
Non-smokers	5	1.89	76	22	..
Smokers	260	98.11	84	37	19

Nationality and Number of Patients

U. S. A.	117	English	3
Italian	35	Swedish	3
Russian	29	Spanish	2
Austrian	16	Turkish	2
Polish	15	Puerto Rican	2
German	9	French	2
Hungarian	7	Danish	1
Scotch	7	Venezuelan	1
Greek	4	Dutch	1
Czechoslovakian	4	Finnish	1
Irish	3	West Indian	1

TABLE IX
FEMALE PATIENTS WITH CANCER OF THE LUNG

Amount of Smoking	Inhalers	Non-inhalers	Total (Average %)
Minimal	2	3	33
Moderate	8	1	59
Heavy	1	0	8

Female Patients with Cancer of the Lung. In studying the thirty-six female patients with histologically proved cancer of the lung there were twenty-one non-smokers (58 per cent) and fifteen smokers (42 per cent).

Table IX shows the smoking habits with relation to inhaling in female patients with cancer of the lung. We see that most of the smokers were minimal to moderate in their use of tobacco. The youngest female patient with cancer of the lung was thirty-one years old and the oldest seventy-two years old. About half the patients were born in the United States and no racial preferences were found. (Table X.)

In one series indicating the smoking habits of the women only 18 per cent were smokers and most of them were minimal smokers. There were slightly more than twice the number of smokers in the cancer group as compared with the controls, and 58 per cent non-smokers in the cancer group as compared with the 82 per cent non-smokers in the controls. Although the number of these patients is relatively small, the influence of smoking in the background of some patients must be of significance.

TABLE X
AGE AND NATIONALITY OF FEMALES WITH CANCER OF THE LUNG

Lung Cancer	Cases		Age		
	No.	Per cent	Oldest	Youngest	Average at Start
Non-smokers	21	58	71	31	..
Smokers	15	42	72	40	21

Nationality and Number of Patients

U. S. A.	15	Irish	1
Italian	4	Romanian	1
Austrian	6	Hungarian	1
Russian	4	Polish	1
Puerto Rican	2	Czechoslovakian	1

It is worthy of note that the number of cases of carcinoma of the lung in the female patients in the last twenty years at Memorial Hospital has been increasing very slowly, in comparison with the marked increased incidence of this disease in the male. The ratio of males to females in this series is more than 7:1.

COMMENTS

The data presented indicate strongly that there is an association between heavy chronic smoking and cancer of the lung. However, further studies are necessary to furnish more precise estimates of the risk involved in smoking. It is necessary to find a large segment of non-smokers and follow them over the years to see in what number cancer of the lung will develop. Such studies are being undertaken by the American Cancer Society[14] and in a few years will provide fruitful information. There is a large number of physicians who believe that the idea of establishing a causal relationship between tobacco smoking and lung neoplasm is erroneous.

Inasmuch as there are serious dissenting opinions we will try to evaluate some of the more pertinent criticisms. As already pointed out the transfer of conclusions from production of skin tumors in animals with tobacco condensates to human cancer is very difficult and more controlled research is needed. The rise in lung cancer in the male sex only is of particular significance because of the marked smoking habit differences in the two sexes, since only in the last few years have the number of women smokers increased. With the length of exposure usually found being over twenty years, a rise in lung cancer may be expected in women if these theories are correct. The apparent stabilized incidence of cancer of the larynx is quoted as a reason that smoking is not important in the etiology of tumors of the lower respiratory tract. However, this may be the result of individual predisposition and there is much statistical proof that heavy tobacco smoking is related in some fashion to the cause of lung cancer.

Critics have pointed out that the methods of reporting may involve two possible errors, namely, predetermination in obtaining a clinical history and a selected sampling of both patients and controls. Doll and Hill[8] thought that they had avoided these pitfalls because a large number of patients believed to have lung cancer at the time of interview later turned out not to have the disease, and yet the smoking habits of this group were distinct from the habits of the true lung cancer group. This is especially true in the Memorial Hospital series in which the controls are from the Thoracic Clinic. Most studies have also taken the sampling from general hospital population in both urban and rural areas or from large autopsy series in which sampling bias was not a factor.

The magnitude of this public health problem now coming into sharper focus with studies on healthy adults of a prospective follow up nature will certainly demand preventive measures and attempts to acquaint the public with both the facts and the fancies of this problem. Many believe that the public should not be put in panic by general statements, but even the critics admit that tobacco smoking can be a factor in sensitive individuals.

Our results parallel the statistics of the recent literature in that a much larger number of smokers were found in the group with cancer of the lung than in the control series.

Most of the male patients with this disease were heavy smokers, but the women were mostly minimal or moderate smokers. Using the method of Cornfield[7] in our present series for calculating the prevalence rate of cancer of the lung per 100,000 men, we found that the estimated prevalence rate for cancer of the lung in smokers is five times that of non-smokers. This is in close agreement with the findings of Doll and Hill. All this evidence points to the important role of tobacco in the etiology of lung cancer, but it does not indicate that it is the sole causal factor or that it is effective in a non-sensitive individual.

SUMMARY*

1. Our study adds to the evidence of the great increase in lung cancer which has become the most common cancer in men and, in some parts of the world, accounts for one-third of all cancer deaths in men.

2. Occupational hazards such as exposure to uranium ores, chromates and asbestos have been shown to increase the incidence of lung cancer. Atmospheric pollution is thought by some to be a factor in the recent increase of this disease.

3. Experimental attempts to reproduce lung cancer with tobacco smoke condensates have up to the present demonstrated only that there is a carcinogenic agent in tobacco smoke which produces tumors on the skin of mice.

4. Cigarette smoking, when quantity and chronicity are considered, represents an additional carcinogenic factor in the inception of primary squamous carcinoma of the lung and the risk of its developing increases in proportion to the amount smoked. The specific carcinogenic agent in tobacco smoke has not yet been found and it seems that pipe and cigar smoking is less likely to be of significance. This may be associated with the habit of inhalation which may prove to be of paramount importance in the etiology of lung cancer.

5. On the basis of the figures of this series the estimated relative prevalence rate of lung cancer in 100,000 male smokers is five times as great as in a non-smoker group.

6. Early diagnosis should lower the mortality and lead to a better survival rate. Prevention, however, depends upon the identification and elimination of the carcinogen believed to be in tobacco and the more complete study of the other possible etiologic factors in this disease.

* Certain parts and tables of this article are from Watson, W. L. and Conte, A. J. Smoking and lung cancer. *Cancer*, vol. 7, 1954.

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Preclinical Bronchogenic Carcinoma

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LESS than 10 per cent of lung cancer patients seen by thoracic surgeons survive five years. The same grim situation is true for cases found by current survey methods.[1] Is the poor prognosis due to delay in detection or is it inherent in the tumors themselves? The answer is not yet available and will not be until concerted efforts result in a better detection program.

While the characteristics of "early" lung cancer have not yet been clearly delineated, let us define "preclinical bronchogenic carcinoma" as lung cancer before its clinical recognition. A study of lung cancer in this phase may contribute to earlier detection.

With this definition in mind, preclinical lung cancer may be classified as follows:

I. Asymptomatic
   A. Without recognizable roentgenographic abnormalities
   B. With recognizable roentgenographic abnormalities
      1. roentgenographic changes missed
      2. roentgenographic changes noted
II. Symptomatic
   A. Clinician not consulted
   B. Clinician consulted
      1. Physician failure to recognize possibility of malignancy
      2. Physician alert to possibility of malignancy
         a. patient refusal of adequate study
         b. patient acceptance of adequate study

There must be in the natural history of every lung cancer a period of indeterminate length during which the patient has no symptoms attributable to the new growth and, because of minuteness of size, the malignancy cannot be seen radiologically. For the patients at this stage of tumor growth there is no possibility of diagnosis since, even though such tests as the Penn-Dowdy serum flocculation test may screen them out as suspect, there is no current possibility of determining the site of such very early cancers.

However, there is a group of asymptomatic lung cancer patients who have abnormal roentgenograms. In our experience, about 10 per cent of survey-detected carcinoma occurs in persons without symptoms. This is the most important segment of proved cases since a high proportion of asymptomatic patients are resectable and may survive five years. Since the highest prevalence of primary bronchogenic carcinoma is among men over forty-five (Table 1) it is feasible to urge asymptomatic men in this age group to report for survey films every six months.

TABLE 1
PREVALENCE PER 100,000 OF PROVED CASES OF BRONCHOGENIC CARCINOMA* BY SEX AND AGE

Sex and Age	No.	Proved Broncogenic Carcinoma	Rate per 100,000
Under 45 years:			
Females	58,605	1	2
Males	56,116	3	5
Total	114,721	4	3
Over 45 years:			
Females	10,858	1	9
Males	16,577	47	284
Total	27,435	48	175
Over-all total	142,156	52	37

* Based on 142,156 individuals x-rayed at two official Philadelphia Units: Unit 1: total 1947, foodhandlers only 1949 through 1952; Unit 3: total 1949 through 1952.

With dual readings of films[2,3] we believe semiannual chest roentgenograms or photofluorograms to be the most effective method for detecting those tumors so peripherally situated as to be surrounded by ventilated pulmonary tissue. This group has the best prognosis. Such patients usually have negative bronchoscopic and cytologic studies and a high resectability rate. If the tuberculin test is positive and

calcium is present in nummular lesions, it seems safe to assume a tuberculous etiology. Otherwise, exploration is mandatory if the patient seems able to withstand the procedure. The difficulties here are those involved in persuading the patient to accept hospitalization in the absence of symptoms.

Despite the best efforts, a few small tumors will be missed in this group because of overlying structures or the difficulty of distinguishing them from adjacent pleura or other shadows of similar homogeneous density. In the study of 100 survey lung cancer cases referred to previously,[1] there were twenty-nine patients on whom previous "negative" films were available for review. Of these, sixteen had erroneously been classified as negative. Five of these were still without symptoms at the time new photofluorograms were recognized as abnormal. Despite delays in recognition, two of the five asymptomatic men were resected and are alive more than five years after the first truly abnormal film.

What percentage of lung cancer cases have symptoms? One of our studies was made on all proved cases out of a large basic group x-rayed with follow-up centered on those with photofluorographic abnormalities. Of a series of 100 cases, 90 per cent had symptoms.[1] However, such information was elicited on interview *after* the film abnormalities had been noted.

In an effort to study more adequately the time relationships between symptoms and roentgenographic abnormalities, the Philadelphia Pulmonary Neoplasm Research Project[4] began operating in December, 1951. The men over forty-five who join this Project are not a random sample but they are interviewed in regard to symptoms before their films are developed so that we are able to correlate symptoms with x-ray changes in the whole group, not just for those with carcinoma. Among the first 3,006 men over forty-five years of age who entered this Project during the first two years of operation, twenty-eight proved bronchogenic carcinomas were diagnosed over a follow-up period of six to thirty months. Not one of these men was without any symptom. The prevalence of cancer according to five major symptoms is presented in Table II. It should be noted, however, that, among the twenty-eight cases in this preliminary presentation of the Philadelphia Pulmonary Neoplasm Research Project, findings differed from routine surveys only in the availability of data from a questionnaire. Therefore, we may anticipate that the fate of these patients will not be better than that of other survey-detected cases. As the study progresses, there will be cancer cases among those whose original films were negative. To date there has been only one such case. In this instance unilateral wheeze preceded the photofluorographic abnormality by nineteen months.

TABLE II
PRIMARY BRONCHOGENIC CARCINOMA ACCORDING TO THE PRESENCE OF FIVE MAJOR SYMPTOMS*

Symptoms†	No.	Per cent of 3,006	Proved Carcinoma	
			No.	Per cent
None of five major symptoms present	1,977	65.8	7	0.4
Cough for months or years	787	26.2	17	2.2
Worsening cough	108	3.6	5	4.6
Hemoptysis	151	5.0	6	4.0
Unilateral wheeze	113	3.8	1	0.9
Weight loss of more than 10 pounds	227	7.6	7	3.1

Note: Follow-up to June 3, 1954.
* Among the first 3,006 men entering the study between December 4, 1951 and December 3, 1953. Philadelphia Pulmonary Neoplasm Research Project.
† Categories not mutually exclusive.

There is no characteristic syndrome of lung cancer, the symptomatology depending on the site of origin, relationship to nerves or vital structures, rapidity of growth, etc. Therefore, it is difficult to devise the needed educational program for lay persons. It does seem that men over forty-five could well be advised to seek medical consultation periodically, and certainly when respiratory symptoms persist or worsen. In our series of survey-detected cases, almost half failed to report to a physician despite the presence of symptoms. Only when patient delay is markedly reduced can we hope to so expedite the diagnosis and treatment of this disease as to assess its curability.

What of the 40 per cent of proved cases who do seek medical advice? It is unfortunate that many physicians fail to consider the possibility of malignancy. Perhaps one should not be

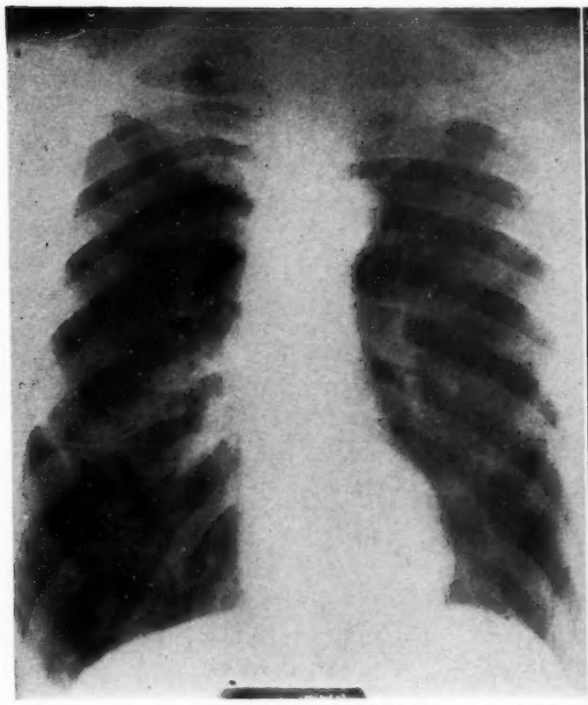

FIG. 1. F. B., a fifty-six year old Negro man, had a 70 mm. photofluorogram on July 26, 1948, interpreted as minimal tuberculosis of indeterminate activity because of infiltrations in the right mid-lung and left apex. No note was made of the localized emphysema in the upper half of the right lung.

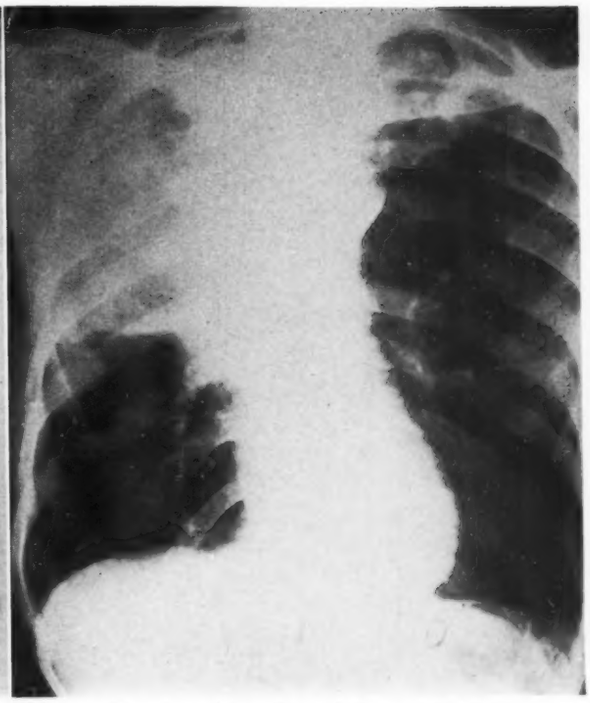

FIG. 2. Same patient. A 14 by 17 roentgenogram taken at time of admission to a teaching hospital (January 18, 1950). Atelectasis due to bronchogenic carcinoma. Patient explored, found inoperable. He had both anaplastic bronchogenic carcinoma and active pulmonary tuberculosis. Ten consecutive sputums were positive for acid-fast bacilli.

impatient because, from the viewpoint of the family physician, lung cancers, though increasing, are not as frequent an explanation of respiratory symptoms as the pneumonias, bronchiectasis and, at lower socio-economic levels, tuberculosis. There is a problem as to whether or not patients will accept recommendations for extensive study. Here is another fertile field for lay education. Careful radiologic study is certainly practicable for all men over forty-five with respiratory symptoms and represents the minimal indicated investigation. If films are negative, and symptoms persist, cytologic study of sputum or bronchial secretions is as important a procedure for cancer detection as is examination of sputum for tubercle bacilli in tuberculosis.

It is our impression that tumors originating in the larger bronchi give rise to symptoms of cough relatively early. Certainly, by the time pneumonitis occurs, the disease has progressed to the point where the size of the tumor is sufficient to permit suppuration distal to partial obstruction. Many patients with advanced malignancies have histories of one or more episodes of "viral pneumonia." It is a sound plan to re-ray every pneumonia patient until a completely negative x-ray is obtained. Even then, the patient should be advised to return at once if symptoms recur and, in the absence of symptoms, to report for semiannual roentgenograms.

As Overholt pointed out years ago, lung cancer is a masquerading disease. Presenting complaints are often shoulder or arm pain, arthritis, hoarseness or other symptoms not immediately pointing to the chest. A great achievement would be made if *all* patients consulting physicians had annual chest x-rays and male patients over forty-five had semiannual radiograms.

It is important to realize that it is not possible to give a pathologic or bacteriologic diagnosis by roentgenographic studies alone. Even such outstanding radiologists as Newell, Chamberlain and Rigler[5] in a carefully controlled study failed to find a reliable classification of the roentgenographic appearance or quality of

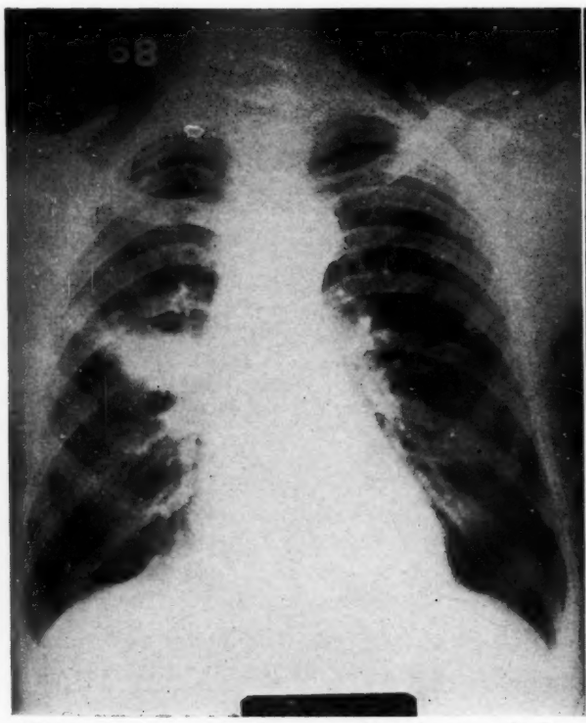

FIG. 3. S. W., a sixty-five year old white man, had a 70 mm. photofluorogram on March 8, 1948, because of cough and hemoptysis. Film interpreted as "suspect neoplasm." Emergency hospitalization arranged.

FIG. 4. Same patient. A 14 by 17 roentgenogram taken at time of cerebral accident (August 24, 1951) revealed increase in size of right hilar mass and volume shrinkage of right upper lobe. Patient died on October, 21, 1952.

a tuberculous pulmonary lesion. Although we know of no similar study of proved cancer cases, it has been our experience that only a little more than one-third such cases detected by survey methods were suspected of malignancy on the basis of their photofluorograms. Almost as high a percentage were thought to have tuberculosis alone. A quarter of the cancer patients had lesions that had been missed on earlier photofluorograms. Thus, as in all aspects of medicine, there is no substitute for judgment. The radiologic report should be viewed in the light of the over-all picture. Even if tuberculosis is suspected alone and confirmed by the finding of sputum positive for bacilli, if there is clinical or radiologic reason for suspecting concomitant malignancy, further efforts at diagnosis are in order. Ten per cent of our survey patients had active tuberculosis as well as proved bronchogenic carcinoma. We have a case in which, because of concentration on the presence of obvious densities suggesting tuberculosis, obstructive emphysema was missed (Fig. 1) and the patient allowed to progress to lobar atelectasis (Fig. 2) before exploration was attempted only to reveal inoperable cancer and active tuberculosis.

In another case, a man admitted as an emergency case to a teaching hospital because of a mass at the right hilum (Fig. 3) was discharged on the basis of one specimen of bronchial secretions positive on smear for tubercle bacilli. He was treated at home for tuberculosis until cerebral metastases developed from his carcinoma at which time his chest film revealed an increase in size of the right hilar mass and volume shrinkage of the right upper lobe. (Fig. 4.) Retrospective investigation of the records revealed that the culture from the specimen collected bronchoscopically had not been positive but this report had gone to the Record Room and had been appended to the chart without any physician's having seen it. No other positive sputum had ever been obtained. Certainly, one unconfirmed smear positive for acid-fast bacilli does not constitute an adequate diagnosis of tuberculosis.

In summary, while the present five-year survival rate from bronchogenic carcinoma is less than 10 per cent, we need not be pessimistic

about the results of resection because we are not yet availing ourselves of all current facilities for earlier diagnosis. A study of proved lung cancer cases at the time of clinical recognition suggests that a better prognosis may be possible with routine semiannual chest x-rays on asymptomatic men over forty-five, a program of lay education to encourage symptomatic men in this age group to seek prompt medical advice, and a heightened level of physician suspicion in regard to male patients over forty-five.

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Pulmonary Cytology

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A CYTOLOGIC laboratory for the examination of pulmonary secretions is a useful and almost necessary adjunct in a diagnostic center which deals with diseases of the thorax. My colleagues and I have found it of inestimable aid in the diagnosis of obscure carcinoma of the lung. It is unfortunate that cytologic study is such a time-consuming procedure, because if it were not it would be exceedingly useful in the detection of unsuspected pulmonary carcinoma, inasmuch as sputum can be raised from the vast majority of lungs.

However, attempts to mechanize the procedure have not proved too successful. As it is now, because of the personnel-time factor involved, it is a costly affair. Most laboratories have utilized technicians to scan the smears of sputum and bronchial secretions and to spot any abnormal cells. This is of inestimable aid in decreasing the time expended by the physician cytologist in examination of the smears of sputum or secretion. It means, of course, that the negative reports are essentially the responsibility of the technician. However, the positive reports become the responsibility of the cytologist. A year's training is necessary in order to make a technician capable of recognizing suspicious-appearing cells in bronchial material. A longer period of training is preferable and certainly leads to increased competency on the part of the technician scanner.

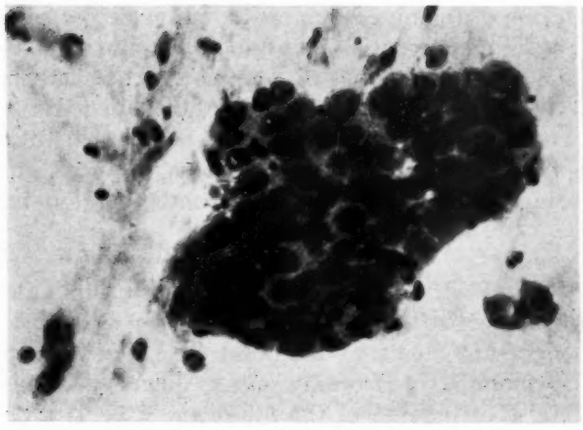
The laboratory of pulmonary cytology at the Mayo Clinic has been organized so that sputum and pulmonary secretions or washings are examined. The sputum is collected in bottles which contain 95 per cent ethyl alcohol. This bottle is given to the patient with instructions to produce sputum from the lungs and not to put saliva into the bottle. A twenty-four-hour specimen is not necessary. Five smears are made at random from the sputum. Selection of the grossly bloody portions of sputum apparently does not increase the incidence of positivity of the smears for cancers, nor does the finding of whitish pieces aid. In our laboratory the smear method rather than paraffin sections has been utilized because of the ease of preparation and also because more material can be examined by this particular method. Our staining technic is that of hematoxylin and eosin rather than any of the trichrome technics that have been employed by others. The diagnosis of anaplastic cells does not appear to be aided by the use of special stains inasmuch as the nucleus is the structure essential to the diagnosis anyway.

RESULTS

During the six years of operation of our laboratory for pulmonary cytology we have reported positive findings in 1,600 cases. In 76 per cent of these cases the positive diagnosis of malignant cells was made from examination of sputum, while in 39 per cent it was made from bronchial secretions. Obviously study of both sputum and bronchial secretions gave positive results in some cases. In 1.7 per cent of this entire group the diagnoses have been considered to be false positive.

The results of cytologic examinations in our laboratory have been reported either as positive or negative on a purely objective basis. The history has not been available during the examination of the suspected material. This seems exceedingly wise to us. In certain cases in which the diagnosis was considered at first to be falsely positive, the patient has later been proved to have cancer of the lung. Other patients are still awaiting an answer. Temporarily these results have been called false positives. The following case illustrates this:

The patient, a sixty-three year old man, stated on admission to the clinic that he had been coughing and wheezing for six months. Wheezes were expiratory and inspiratory and bilateral. A roentgenogram of the chest showed fibrous and calcified lesions in apices of both lungs which were thought to be due to ancient tuberculosis. Two bronchoscopic examinations were negative but malignant cells were found



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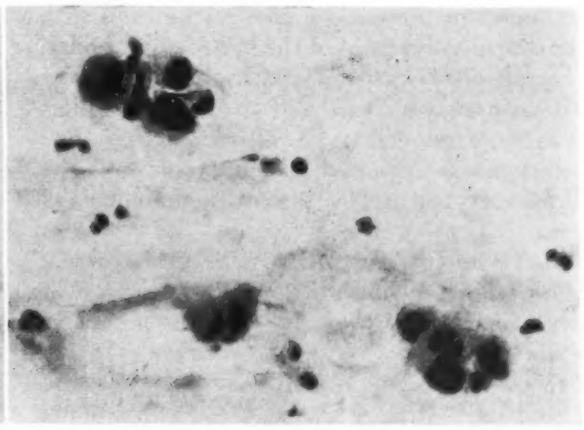

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FIG. 1. A clump of anaplastic-appearing cells in bronchial secretions. This patient has not shown any clinical signs of cancer.

FIG. 2. A clump of cancer cells is shown in sputum.

in bronchial secretions from both the right and left bronchi on two occasions. (Fig. 1.) Sputum was consistently negative for malignant cells. Re-examination one and a half years later showed no change in the status and no development of symptoms suggesting bronchogenic carcinoma. In this case the result must be considered false positive although the cells are very suggestive of malignant cells.

It is very difficult to determine what the false-negative error is in such a series of cases. The false negative error probably is between 30 and 35 per cent in our cases. If this percentage is lowered much, the false positive error increases. In spite of this high degree of false negativity for bronchogenic carcinoma, the procedure is exceedingly valuable.

USES

Examination of sputum and bronchial secretions is most useful in several situations:

1. It is useful in the diagnosis of bronchogenic carcinoma of an upper lobe of the lung because lesions in this location are very difficult and often impossible to visualize bronchoscopically. Frequently a positive cytologic diagnosis gives the only definite evidence of carcinoma in this location before operation.

2. It is useful, too, in the diagnosis of bronchogenic carcinoma which is peripherally situated in the lung. These lesions, however, do not give a high incidence of positive cytologic findings. It is necessary, of course, to have a bronchus communicating with the carcinoma in order to have cytologically positive sputum; and if no such communication is present, the sputum will not be positive.

3. Examination of sputum in the presence of a metastatic lesion is definitely valuable in the diagnosis of malignant disease and it frequently may give the first positive evidence that a metastatic lesion exists.

4. In cases of alveolar cell tumor cytologic examinations usually give positive findings. The more anaplastic the cell type in this disease, the more readily the tumor cells are recognized in sputum and bronchial secretions. Frequently the cells are found in clumps which have broken off.

The main usefulness of cytologic examination of pulmonary secretions lies in the diagnosis of bronchogenic carcinoma. The following case illustrates this:

The patient, a sixty year old man, had been a heavy cigarette smoker for many years but his cough had become worse in the last six weeks before admission. There had been no hemoptysis. Physical examination gave negative results. A routine roentgenogram of the chest and results of other examinations were essentially negative. Examination of sputum revealed malignant cells. (Fig. 2.) On bronchoscopic examination no tumor was seen. Bronchial washings from the right side showed carcinoma cells and those from the left side showed none. A stereoscopic roentgenogram revealed a rounded mass in the right lower part of the lung field which in a tomogram appeared to be 2 cm. in diameter. At exploration of the right side of the chest a small tumor

was found in the middle lobe of the lung with extensive involvement of the hilar lymph nodes. A lymph node was removed from the superior mediastinum which proved to be an undifferentiated large cell type of carcinoma. The condition was regarded as inoperable and the thorax was closed. The patient died eight days later.

We have found that results of cytologic examination are most likely to be positive in cases of small cell or "oat" cell carcinoma of the lung and next most likely to be positive in cases of squamous cell carcinoma of the lung. This is true because these carcinomas involve the larger bronchi and produce ulceration of the mucosa in most instances. We have not found results of cytologic examination to be positive in cases of adenoma of the lung in which bronchial mucosa over the adenoma is intact. This observation has been of help in distinguishing between adenoma of the bronchus and small cell undifferentiated carcinoma.

SUMMARY

The cytologic examination of sputum and bronchial secretions and washings is a valuable procedure in the diagnosis of bronchogenic carcinoma. It also may give evidence of metastatic carcinoma of the lungs and alveolar cell carcinoma.

Bronchogenic Carcinoma

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IT is generally agreed among pathologists the world over that practically all primary cancers of the lung originate and spring from the basal cell layer of the bronchial mucosa; hence the designation, bronchogenic carcinoma. They may arise anywhere along the course of the bronchial tree from the major stem bronchus to the extreme peripheral or terminal bronchioles. Even one of the rarer forms of bronchogenic carcinoma, the alveolar cell carcinoma which Ewing[1] thought arose from the lining cells of the alveoli, is now considered by Storey et al.,[2] Herbut[3] and Watson[4] to originate in the basal cell layer of the terminal bronchial mucosa. Until recently this type of tumor had always been considered of multicentric origin but the studies of Storey[2] convince him of its unicentric origin. He believes the usual widespread, finely disseminated roentgenographic shadows simulating miliary distribution represent late manifestations of the disease produced by canalicular extension.

Bronchogenic carcinoma possesses characteristics common to all malignant tumors. It is invasive, obstructive and destructive. It tends to ulcerate and to erode, to undergo necrosis, secondary infection and suppuration, and it metastasizes. In the course of its growth it advances boldly into the body of the lung and also protrudes into the lumen of the bronchus. Both of these events profoundly alter the orderly functioning of these structures, especially the relatively small portion intruding into the bronchial lumen. It is the latter which interferes with the normal elastic expansion and contraction of the bronchial wall during the respiratory act. It is the latter which also effects a gradual increasing atresia of the bronchus resulting in a damaging interference with the normal ventilatory properties of the lung and with the drainage of the bronchial airways distal to the growth. Retention of infection follows such increasing obstruction with the consequent development of patchy areas of resolving or organizing lobular pneumonitis. While the obstruction is only *partial*, the resulting pneumonitis is more likely to be resolving in character and intermittent and repetitive in type. If the protruding part is pedunculated in form, a ball-valve (check-valve) mechanism may be set up for a limited period permitting the ingress of air to distal areas on inhalation but preventing its expulsion on exhalation, with consequent establishment of emphysema in those areas. When the obstruction becomes *complete*, the further admittance of air ceases, the air previously trapped becomes absorbed and the emphysematous areas are converted into atelectatic ones. This transition may occur with amazing rapidity. Atelectasis is invariably followed by the development of organizing pneumonitis. If the protruding part of the growth is more sessile in form and slower in growth, organizing pneumonitis is more likely to result, at times even before the obstruction is completed. From these ever-mutating pathophysiologic dynamics arise the marked variations observed in the symptomatology, physical findings and roentgenographic recordings which are so characteristic of this disease.

TYPES OF BRONCHOGENIC CARCINOMA

The more anaplastic among these tumors are characterized histologically by an increase in chromatin content of nucleus, marked evidence of mitosis, loss of cellular polarity and more intensive and accelerated invasive properties. Their behavior is conditioned by their basal cell type. In general there are three basic cell types: the squamous (epidermoid, epithelioma) cell, the small (oat, transitional) cell and the adenocarcinoma. Moersch and McDonald[5] feel justified in adding a fourth group which they call the "large cell type," one including "undifferentiated types" not conforming to the pattern of the first three. Often it is difficult to label a given tumor, for the several types may be identified in different portions of the same mass, in which case the dominant cell type usually determines its role. While having some features in common, the several types

differ with each other in varying degree in malignancy, in location, in duration or tempo of evolution and in modes of metastasizing. These are the factors that determine in so large a measure the prognosis and possible operability of a given case. Accuracy in diagnosis of the type of the neoplasm is therefore most important, for the decision to operate is weighted heavily in favor of the less anaplastic ones.

The squamous cell type comprises about 42 per cent of all bronchogenic carcinoma. It may arise from any portion of the bronchial tree but usually does arise from one of the larger branches of the stem bronchus. It is somewhat slower in its evolution than the other types; slower in narrowing the lumen of the bronchus and thus more likely to produce disturbed ventilatory function. Particularly in this type, retention of infection occurs with the development of areas of pneumonitis or emphysema or atelectasis. The pneumonic areas may temporarily resolve or become an organizing process or undergo suppurative changes and terminate in abscess formation. The prevailing microflora present largely determines this outcome, especially the presence of anaerobes and spirochetes. The growth itself may undergo necrosis and develop within it a suppurative antrum. Death in this squamous cell type often enough results from these complications or sequelae. This type of carcinoma tends to metastasize relatively late and does so more frequently by way of the lymph stream. Superficial adenopathy appears more often in this type. The Pancoast tumor or superior sulcus tumor, occurring not too infrequently, is of this squamous cell group. It is always located in the extreme vault of the thorax and because of its confined quarters tends to bore directly through the bony cage which invests it. In its growth it may exert pressure on the cervical sympathetic nerve giving rise to the typical Horner's syndrome. It is also apt to invade the brachial plexus with the production of considerable pain about the shoulder and down the arm, even at times extending to the fingertips. Atrophy of the muscles of the forearm and hand often co-exists. It is the squamous cell type of bronchogenic carcinoma which furnishes the vast majority of cases suitable for excisional surgery. This is due in part to its relatively slower evolution and in part to its generally later period of metastasizing.

The small cell type (including the undifferentiated cell type, the so-called "oat" cell and the transitional cell tumors) comprises about 33 per cent of all lung cancers. This is the most anaplastic of all such tumors, the most rapid in growth, and hence, the most lethal from a prognostic viewpoint. It is invariably located close to the hilum arising frequently from a major stem bronchus or from one of its immediate branches. It is vigorously invasive, rapidly involving the adjacent tracheobronchial and paratracheal lymph nodes either by direct extension or by way of the lymph channels. This tumor with its tracheobronchial node involvement is very apt to produce a large mass in the mediastinum which exerts much pressure on neighboring structures, such as the superior vena cava, the phrenic nerve, the esophagus or the inferior laryngeal nerve. From such pressure arise symptoms so characteristic of this type: (1) dilation of the superficial veins of the chest, neck and face, and at times edema of these areas, (2) elevation and fixation of the diaphragm, (3) dysphagia and regurgitation and (4) hoarseness or aphonia. Rarely does this type undergo necrotic or suppurative degeneration or produce organizing pneumonic or atelectic charges distal to its location. Death usually occurs before these complications have time to intervene. This is the least resectable of all the types. Death usually comes within three to six months of the presenting symptoms or sign. Remote metastases occur much less frequently than in other types.

The adenocarcinoma type comprises about 25 per cent of these malignant tumors. It is the one most frequently found in the female. It may appear in any part of the lung but is more often peripherally located. It is frequently identified with pleural irritation and effusion, hemoptysis and remote metastases by lymph and blood stream. Metastases to the brain and other structures may occasion symptoms *in advance* of those arising from the parent growth. Because of the more frequent occurrence of metastasis this, too, is a type less often found suited for operation. There is a growing belief among pathologists that the adenocarcinoma cell type is definitely of congenital origin.[6]

The sites of metastases of all types of bronchogenic carcinoma in the order of frequency are: regional lymph nodes (tracheobronchial, paratracheal, supraclavicular, cervical, anterior scalene and axillary), liver, lungs, bones, kidneys, adrenals, pleura and brain. In an

excellent summary Shefts and his associates[7] extol the value of scalene node biopsy as a diagnostic aid. It is believed that the right anterior scalene nodes drain not only the three lobes of the right lung but also the greater part of the left lower lobe and are therefore apt to furnish revealing biopsy material.

PRECLINICAL BRONCHOGENIC CARCINOMA

Before discussing the symptoms of cancer of the lung and their significance, it must be realized and stressed that in a great many instances they are late—often too late—manifestations of the disease. A dormant or "silent" period exists between the formation of the first abnormal cell and the occurrence of the first overt sign. The duration of this period varies with the type of tumor; unquestionably shorter in the more anaplastic types, longer in the more differentiated ones. During this period much damage is often wrought on adjacent structures in the chest and to near or remote organs by metastasis, especially in the case of the small cell and adenomatous types. Sooner or later, before symptoms arise, changes in the lung or mediastinum often occur capable of casting an abnormal shadow in the roentgenogram. The shadow observed may be that of the tumor itself or of an area of localized emphysema, of atelectasis or of organizing pneumonia. The roentgenogram thus renders it possible to detect pulmonary abnormalities in this precious preclinical or latent period, the time most suitable for rational treatment. Obviously, this demands greater utilization of the chest x-ray in the search of the hidden foe, even to the point of instituting mass surveys of all living patients in the Cancer Age bracket of forty-five to sixty-five years but especially of those who have been heavy cigarette smokers over the years. If this practice obtained, many more cases would be discovered at an operable stage and many more lives would be saved or at least considerably prolonged.

SYMPTOMS

In considering the presenting symptoms of this disease, it is important to note that in many cases there is a history of one or several attacks of acute upper respiratory infections often called "flu," "virus pneumonia" or "acute bronchitis." These bouts may be mild or severe, simple catarrhal or suppurative, depending upon the microflora prevailing at the time. Usually fleeting in character, they were formerly considered to be prodromal episodes. Actually they are manifestations of interrupted bronchial drainage and of retained infection culminating in the production of patchy areas of lobular pneumonitis. In the majority of cases the onset is insidious, characterized by symptoms so protean and dissembling in nature as to simulate practically any respiratory affection closely. Overholt has aptly termed cancer of the lung "the great masquerader of pulmonary diseases."

In the course of time definitive symptoms do arise and persist, and they are in order of frequency as follows:

Cough and Expectoration. These occur in about 70 per cent of all cases. The cough at the beginning is often dry and spasmodic, the growth at this time acting as would a foreign body in the wall of the bronchus. The resulting irritation stimulates the mechanism of expulsion, hence the spastic quality of the cough with little or no sputum. Later, as secondary pneumonitis develops or the growth undergoes necrosis and suppuration, the cough becomes a productive one. The sputum, scanty at first, may become profuse and may become purulent.

Pain. The majority of patients experience this symptom some time during the course of the disease. When it does occur, it is usually early and constant and boring in quality, and may interfere with sleep at night. If pleurisy co-exists, the pain is sharp and stabbing in character and much accentuated by deep breathing.

Dyspnea, occurring in slightly less than half of all cases, is occasioned by varying degrees of bronchial obstruction. Areas of emphysema produced by the check-valve mechanism described by Jackson,[8] if sufficiently extensive, may cause dyspnea. The sudden imposition of moderately extensive atelectasis will also give rise to dyspnea, as will massive accumulations of pleural fluid. Rarely is dyspnea toxic in origin.

Wheeze, often accompanying dyspnea, is brought about by varying degrees of bronchial obstruction. Whenever this symptom, dyspnea or both develop for the *first* time in patients after forty-five years of age and *persist*, they should immediately alert one to the possible presence of a bronchial tumor, provided no known cardiovascular or allergic factors are present.

Anorexia. This is a fairly consistent finding at any time during the course of the disease.

Loss of strength and weight is a strikingly variable occurrence, more often late in appearance.

Fever may be present at any time, early or late, intermittent or continuous. It is a product of ulceration, necrosis and secondary infection of the mass itself or of the concomitant pneumonitis.

Hemoptysis, rarely massive, is invariably the result of ulceration and erosion and occurs more often in the adenocarcinomatous or more peripherally located tumors.

Pressure symptoms may develop, such as dilation of the veins of the chest, neck or face or even edema of these parts; dysphagia, hoarseness or aphonia; and x-ray evidence of marked elevation of a diaphragm. These are all the result of encroachment of either the mass itself or its metastatic nodular products on immediately adjacent structures in the mediastinum, namely, the superior vena cava, the esophagus, the inferior laryngeal nerve or the phrenic nerve. Evidence of any one of these invasive manifestations is generally considered a contraindication to resectional surgery. They are more likely to occur with the small cell type of neoplasm because of its invariable close proximity to these mediastinal structures.

Anemia and cachexia are usually late complications.

Pulmonary osteoarthropathy ("clubbed fingers") is occasionally observed in the course of the relatively slower growing masses as in some squamous cell types. Here time permits low grade suppurative processes such as abscess formation and bronchiectasis to develop before other more lethal factors terminate the case; hence it is seldom if ever seen in the small cell or adenocarcinoma types.

PLEURAL EFFUSIONS

Statistical reports as to the frequency of occurrence of pleural effusions vary considerably, ranging from 15 to 45 per cent. They are more apt to occur with the adenocarcinoma cell types and other peripherally located tumors and they reveal the presence of blood in about one-third of the cases. When aspirated the fluid reforms rapidly, affording only transient relief from the pain or dyspnea which usually accompany it. Such fluid is of low specific gravity and low cell count and is distinguished by its low degree of viscidity. Cancer cells may occasionally be demonstrated in the centrifuged sediment, either by cell block or by employing Papanicolaou technic.[9] The absence of acid-fast bacilli in the sediment, determined by repeated smear, culture and guinea pig inoculations, serves as a differential factor.

LABORATORY FINDINGS

There is nothing characteristic about the gross appearance of the sputum. It may run the gamut from clear mucoid expectoration to a greenish gray, foul-smelling purulent discharge. Here again tumor cells may be demonstrated, especially if the Papanicolaou technic[9] is employed. The finding of acid-fast bacilli in the sputum does not, of course, rule out the possible co-existence of a neoplasm, for a tuberculous lesion and bronchogenic carcinoma may occur concomitantly in the same lung or even in the same lobe.

The sedimentation rate is generally increased, usually averaging between 20 and 30 mm. in one hour (Cutler method).

PHYSICAL FINDINGS IN THE CHEST

The findings on physical examination of the chest are naturally conditioned by the stage of evolution of the growth, by its location and by the occurrence of sequelae consequent to the mechanical and biologic alterations which follow in its wake. These latter may range from emphysema to atelectasis, from pneumonitis to abscess with correlative changes in the physical signs. Invariably there is limitation of motion on the affected side. Superficial adenopathy when present may be noted by inspection and palpation, especially in the cervical, supraclavicular or axillary regions. Dilation of the superficial veins or edema may be observed in the region of the upper chest and neck. The percussion note is uniformly dull to flat over the growth or over areas of concomitant pneumonitis or atelectasis. The note may be tympanitic if emphysema is at all extensive. Tactile fremitus is diminished or absent over the same areas. On auscultation the most frequent finding is that of markedly diminished or absent breath sounds over the areas just described. Rales may or may not be present and do not serve as a differential point.

CAUSES OF DEATH

The causes of death in cancer of the lung are many and varied. They are determined largely by the type and grade of malignancy of the tumor. In the relatively slower growing tumors such as the squamous cell type secondary infection and metastases play a major role, with pneumonia, lung abscess and bronchiectasis occurring quite frequently. Asphyxia and cachexia may develop with any type but predominate with the small cell group. Hemorrhage and cardiac decompensation occasionally occur in all forms but slightly more with the adenocarcinoma group, as do metastases to the brain, liver, contralateral lung, kidneys and the long bones.

PROGNOSIS AND TREATMENT

The prognosis is always grave, especially in the more anaplastic types, the small cell and adenocarcinoma types. Rarely indeed is there a postoperative survival of three or more years in these cell types. The outlook is more hopeful in the squamous cell types, but even here the all-determining factor is early discovery, preferably in the preclinical or "silent" period. Where evidence of metastases exists or when bloody pleural effusion is present or where clear-cut symptoms and signs of intramediastinal pressure occur, the prognosis is more grim.

At the present time excisional surgery offers the only possible chance of a lasting cure. Success or failure is directly proportionate to the promptness with which diagnosis is established. It must be stressed that the success of surgical attack is conditioned by the type and grade of malignancy of the growth, its size and location, and of course, the age and general physical condition of the patient. The operations employed are lobectomy or, more often, pneumonectomy. The choice of operation is decided largely by the location of the growth, its extent and, in some measure, by the philosophy of the surgeon. The immediate operative mortality is encouragingly low (10 to 15 per cent), due chiefly to the amazing advancement in operating and anesthesia technics, the judicious use of blood plasma or whole blood and the generous utilization of antibiotics pre- and postoperatively.

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The Roentgen Manifestations of Bronchiogenic Carcinoma

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IN cancer of the lung, cure is possible if the lesion is detected in the early stages, especially before metastases have developed. The importance of early diagnosis cannot be overemphasized. This disease must be considered in the differential diagnosis in every case in which there is an abnormal roentgen appearance in the lungs, particularly in an adult. The early diagnosis of pulmonary carcinoma has been greatly aided by bronchoscopy, intrabronchial biopsy and cytologic examination of the bronchial secretions and the sputum. However, despite advances in diagnostic methods and the tremendous achievements of the thoracic surgeon during recent years, the great majority of patients are seen only when the disease is far advanced and no longer confined to the lungs. The average patient does not seek medical attention until several months after the beginning of his symptoms and usually there is a lapse of six months or more before the diagnosis has been definitely established. By this time the tumor has become so extensive that there is little or no chance of eradicating the disease.

The symptomatology, the findings on clinical and laboratory examinations, and the course of carcinoma of the lung are extremely variable. Symptoms may be absent for long periods of time. The condition may mimic a host of diseases and many cases are treated as tuberculosis, chronic pneumonia, abscess and other diseases. Since these as well as other pulmonary lesions often occur in association with primary carcinoma of the lungs, it is obvious that diagnosis is extremely difficult. Mass x-ray surveys of the chest are uncovering an appreciable number of cases of carcinoma of the lung. In a survey carried out in Boston a total of 536,000 patients were examined. Approximately one case of primary carcinoma was found in every 20,000 roentgen examinations. These patients in most instances had no complaints referable to the chest.

In many patients there are no symptoms which would lead one to even think of the possibility of disease of the lungs. This is particularly true of cases which arise in the region of the hilum of the lung, as these neoplasms tend to remain entirely asymtomatic until the lesion has eroded the bronchial mucosa and encroached upon or obstructed the lumen of the bronchus.

Since clinical diagnosis is so difficult, the clinician must avail himself of every diagnostic aid at his disposal. The roentgen findings are frequently the first and most important factors in contributing to early diagnosis. Sagittal roentgenograms, best made stereoscopically, must be supplemented by lateral, oblique and decubitus views. Fluoroscopy is essential. Overexposed films with the Bucky diaphragm are very important to visualize lesions behind the heart and for observation of the bony structures. Roentgenograms in full expiration, in addition to those usually made at the end of inspiration, may be helpful to demonstrate areas of localized emphysema or atelectasis. Repeated examinations at intervals of a few days or weeks to show the progression of the changes may be very important in arriving at a final conclusion. Bronchography, body section roentgenography, Bucky chest films and other aids must be utilized by the roentgenologist in every case. Kymography may help in differentiating a tumor of the hilum or mediastinum from an aneurysm of the aorta and other lesions which may closely simulate carcinoma of the lung. Bronchoscopy is of value in the accessible type of lesion, but is of no avail in tumors of the apices and other inaccessible areas. Tumor cells may be found in the sputum or in the fluid removed by tapping and must be carefully searched for in every instance. Aspiration biopsy under fluoroscopic control may be helpful. Pneumothorax after the removal of pleural fluid may reveal a mass which was previously obscured. An absolutely definite

diagnosis of carcinoma of the lung can be established only by the demonstration of the character and type of the neoplasm after microscopic examination. Many other conditions may closely simulate carcinoma of the lung; and despite an apparently characteristic clinical history and roentgen findings, errors in diagnosis will be made unless the findings are confirmed by the microscope. Thoracotomy may be necessary in order to establish a diagnosis. It is generally agreed that with the low mortality in thoracic surgery today, exploratory procedures should be utilized much more freely than previously if the disease is to be eradicated and the percentage of cures increased.

ROENTGEN MANIFESTATIONS

The roentgen examination affords the most dependable and accurate method of establishing the diagnosis of carcinoma of the lung. It must be stressed that the shadows produced on the roentgenogram indicate merely the gross pathologic condition. The roentgen study enables the observer to determine the size, density, outline and location of the changes in the lungs. It is not always possible to translate the gross manifestations into a microscopic picture and there may be great difficulty in arriving at a definite and conclusive diagnosis on the basis of the roentgen study alone. The x-ray affords the only means of visualizing the lesion and making an early diagnosis in tumors which are beyond the reach of the bronchoscope and outside the scope of other laboratory methods of examination. Roentgen methods of study demonstrate bronchiogenic carcinoma in about 98 per cent of the cases and establish the diagnosis in over 80 per cent of these patients.

The roentgen picture varies according to whether the tumor is located in (1) the hilum; (2) the central or parenchymal portion of the lung; and (3) the peripheral or subpleural region.

Hilar Tumor. This type arises in the proximal portion of the bronchial tree, usually in the region of the root of the lung. Since the bronchus is quite wide at this point, the early stages of the disease may produce little or no change on the roentgenogram. As the tumor enlarges, definite manifestations develop. Lesions which grow outside the lumen of the bronchus produce a localized, sharply defined area of increased density in the region of the root of the lung. The margins of the mass tend to be lobulated. Those which extend within or along the wall of the bronchus tend to have an irregular, poorly defined margin. The density in the roentgenogram is usually unilateral and sharply defined. The tumor is apt to occlude the bronchus and cause atelectasis with collapse of the lung distal to the point of obstruction. If the main bronchus is involved, the entire lung collapses. Occlusion of a segmental bronchus results in collapse limited to the segment of the lung supplied by the affected bronchus. The degree of atelectasis and the size of the atelectatic area are not an index of the size of the tumor. Atelectasis is manifested by increased density over the involved portion of the lung, marked narrowing of the interspaces, displacement of the heart and trachea to the affected side and elevation of the diaphragm, frequently marked in degree. The unaffected portion of the lung or the opposite lung in cases of complete collapse show emphysema. The emphysema is present in the portion of the lung adjacent and immediately distal to the site of the neoplasm and may be due to compensatory changes or a valve-like narrowing of the lumen of the bronchus which permits air to enter the lung more freely than to leave, resulting in localized hyperaeration. An early neoplasm of the lung which is not of sufficient density or is too small to produce a definite shadow in the roentgenogram may produce areas of localized emphysema, and careful observation of these permits an earlier diagnosis than would otherwise be possible. (Figs. 1 and 2.)

Tumors of Parenchymal Origin. Bronchiogenic carcinomas which arise in the secondary or tertiary bronchi lie deep in the parenchyma of the lung and are usually completely surrounded by lung tissue. The growth may extend along the bronchial wall outside of the lumen of the bronchus or grow into the bronchial lumen. The lesion is manifested by a rounded or ovoid area of increased density. The margins of the growth are smooth and sharply defined in some cases; in others there is irregular extension into the adjacent lung tissue. These tumors frequently remain asymptomatic for considerable periods of time and may become quite large before producing symptoms. These are the type which are discovered on routine chest roentgenograms or during mass surveys, the patient being unaware of the existence of anything of an abnormal

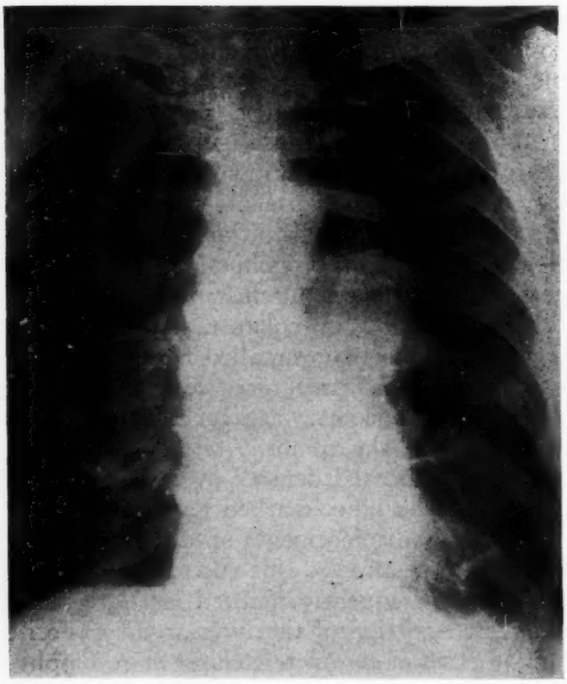


FIG. 1. Bronchiogenic carcinoma. There is a sharply defined area of increased density in the left parahilar region. There is emphysema, manifested by increased radiance, in the lung adjacent to the neoplasm.

FIG. 2. Bronchiogenic carcinoma. Advanced carcinoma involving the upper half of the right lung. The upper right interspaces are narrowed and the trachea is deviated to the right, indicative of atelectasis. The small, irregular area of increased density in the left mid-lung field adjacent to the left hilum represents a metastatic nodule.

nature in the chest. Abscess formations frequently develop. The lesion differs from the usual inflammatory abscess of the lung in that it has a denser and thicker wall and its margins are more irregular. A fluid level in many instances is present within the abscess. The parenchymal type of carcinoma may also occur as a diffuse, nodular reticulation throughout the lung fields, closely simulating the metastatic lymphangitic type which spreads through the lymphatics and is very highly malignant. The roentgen picture closely simulates pneumonitis, bronchitis and bronchiectasis and errors in diagnosis are very common.

Tumors Arising in Peripheral Portions of Lung. Primary carcinomas of the lung originating in the extreme peripheral portion of the lung have their point of origin in the smaller bronchioles adjacent to the visceral pleura. In the early stages there is a rounded or irregular area of increased density, most commonly in the axillary or basal portion of the lung. The tumor may be sharply demarcated with clearly defined margins or present hazy, irregular borders which extend in infiltrative fashion into the adjacent lung tissue. The growth may originate in any portion of the lung, and those situated in the region adjacent to the interlobar septa or the mediastinal surfaces of the lung often appear to be hilar or central in origin. By use of oblique and lateral roentgenograms and roentgenoscopy, the peripheral location of the mass can usually be determined. Tumors arising in the apical portion of the lung and which involve the apex and upper lung field are termed the superior sulcus tumor of Pancoast. This type of carcinoma of the lung is particularly apt to produce localized destruction of the ribs and is associated with the presence of Horner's syndrome in many instances. There is a homogeneous density involving the apex and the upper third of the lung field with destruction of a portion of one or more ribs. In contrast to the other types of bronchiogenic carcinoma the apical lesions frequently produce very striking and severe clinical manifestations which are in marked contrast to the relatively small size of the neoplasm. Because of involvement of the pleura, pleural effusion frequently develops. The fluid is apt to be bloody. (Fig. 3.)

The size of the tumor in primary carcinoma of the lung may vary from miliary to extremely large. The mass may be rounded, irregular or wedge-shaped. With the passage of time the tumors enlarge both centrally and peripherally. In some instances there is a narrow band of density extending from the mass in the lung to the hilum. The hilus nodes are usually not involved until late in the parenchymal types of primary carcinoma; the same is true of the peripheral type. The neoplasm may in some cases be manifested as a nodular dissemination or a diffuse reticulation in the lung rather than as a localized mass. Abscess formation is usually due to perforation of the bronchial walls with subsequent necrosis. Lobar consolidation may precede or accompany the abscess formation. Atelectasis and fluid are frequent occurrences in tumors of the lungs and in many cases obscure both the primary growth and areas of destruction in the bony thorax. Marked thickening of the pleura is also common and may simulate pleural effusion clinically and roentgenographically. The displacement of the mediastinal structures and the changes in the bony thorax which occur in fluid or atelectasis may be modified or absent in the presence of marked infiltrations or thickening of the pleura. Bronchiectasis is frequently concomitant with primary carcinoma of the lung. Pneumonitis, unresolved pneumonia and chronic tuberculosis may occur and may mask or obscure the clinical and roentgen picture for long periods of time. Elevation of the diaphragm with paradoxic excursion is indicative of paralysis of the phrenic nerve by invasion of the neoplasm. Metastases may occur to the same or opposite lung, hence the fact that there are multiple tumors in the lungs does not exclude the possibility of bronchiogenic carcinoma.

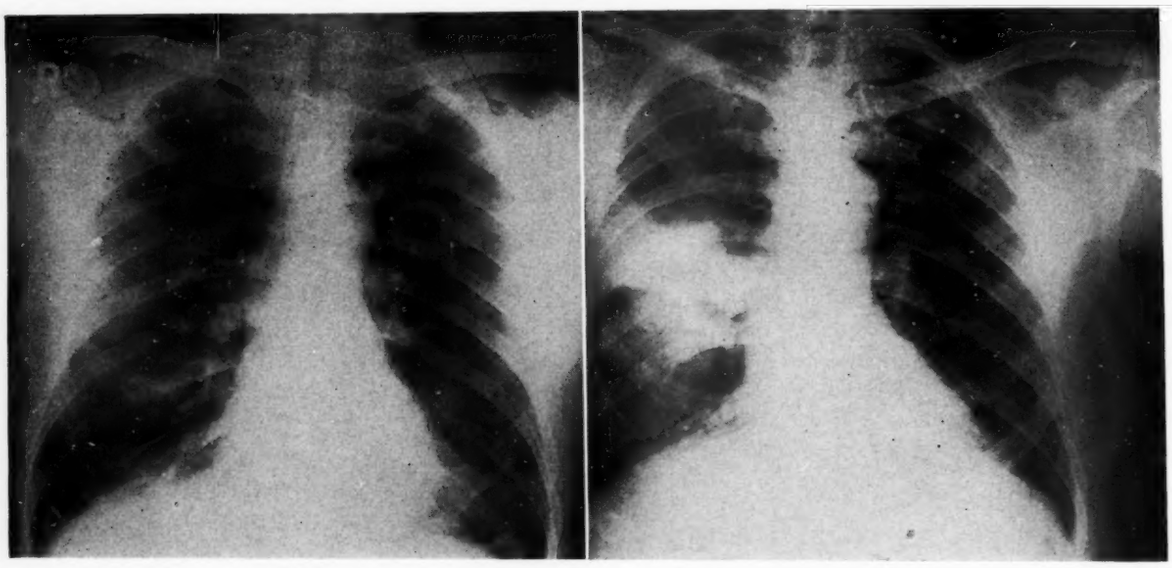
Bronchography is of great value in the diagnosis of bronchial occlusions, abscess formations and bronchiectatic changes. Body section roentgenography and overexposed films with the Bucky diaphragm are of aid in the demonstration of narrowing or obliteration of the bronchus, cavitations, and changes in the ribs, scapulae, clavicles or vertebrae as well as lesions which may be obscured by the overlying heart or mediastinal shadows. Therapeutic pneumothorax, particularly after withdrawal of pleural fluid, may outline masses which are obscured and also show other important

FIG. 3. Advanced carcinoma of the right lung. The upper half of the right lung is involved by advanced bronchiogenic carcinoma. The right hilum is markedly enlarged and irregular. There is atelectasis on the right, the upper interspaces being narrowed and the heart and trachea being deviated to the right.

changes otherwise not demonstrable. Laminagraphic studies are especially indicated to show changes in the bronchus and to demonstrate masses or cavitations which otherwise would be overlooked or obscured. Serial roentgenograms at intervals of a few days or weeks to demonstrate the progression constitute a most important aid in diagnosis. However, it is not advisable to wait more than two or at most three weeks between the examinations, as longer intervals may permit marked extension of the tumor and the development of metastases. (Fig. 4.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis must include a host of lesions. Tuberculosis, bronchiectasis, pneumonia, lymphoma, metastatic neoplasm, postradiation fibrosis and many other conditions must be considered. Lipoid pneumonia, the virus types of pneumonia and the nonspecific granulomas may produce changes which closely simulate primary carcinoma of the lung. Lung abscess associated with homolateral displacement of the heart and mediastinal contents or localized emphysema distal to the abscess should always raise the question of bronchiogenic carcinoma. Syphilis and



4A 4B

FIG. 4. Bronchiogenic carcinoma. A, the right hilus shadow is slightly enlarged and there is slight haziness with prominence of the markings in the right parahilar region. B, Same patient, seven months later. There is an extensive, irregular area of increased density involving the right lung field in the parahilar region. At the time of the first roentgen study (Fig. 4A) the patient had a severe cough. The diagnosis of carcinoma of the lung was suggested and re-examination was advised within three to six weeks. He failed to return until seven months had elapsed, at which time advanced bronchiogenic carcinoma was clearly manifested.

tuberculosis may closely simulate carcinoma of the lung. The tuberculoma, which produces a solitary mass in the lung quite similar in appearance to carcinoma of the lung, is usually considered a benign lesion. However, all tuberculomas are potentially dangerous because of the great probability of subsequent breakdown with the dissemination of tubercle bacilli. This results in rapid and widespread dissemination of the disease. The principal benign tumors which may cause confusion in diagnosis are the lipomas, neurofibromas, chondromas, adenomas, hamartomas and cysts. These lesions do not show rapid progression on subsequent roentgen studies. The laboratory examinations are also negative. Several vascular types of lesions are occasionally confused with carcinoma. An infarct may produce an area of density in the lung which simulates carcinoma. The history is usually important and establishes the differential diagnosis. Studies after an interval of one or two weeks show resolution and diminution in the size of the infarct. A broncholith due to a foreign body may produce bronchostenosis with atelectasis. Substernal thyroid may be differentiated by the displacement and narrowing of the trachea which usually occurs in this condition. Metastatic lesions may in rare instances be solitary and sharply defined and produce pictures which very closely simulate primary carcinoma of the lung. The determination of the primary site of the growth is usually the important factor in establishing the diagnosis. Other diseases, particularly tuberculosis and pneumonia, can occur simultaneously with bronchiogenic carcinoma and the establishment of one diagnosis does not preclude the presence of tumor.

The possibility of carcinoma of the lung must be borne in mind in every obscure pulmonary lesion. Only by constant care and alertness will early diagnosis be possible. Routine periodic roentgen study of the chest, preferably at intervals of six months to a year, and prompt attention to pulmonary symptoms are of the utmost significance in reducing the mortality from this malady.

Detection, Selection and Resection in Pulmonary Carcinoma

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DETECTION of asymptomatic pulmonary carcinoma is possible through radiologic screening. Selection of resectable cases requires prompt thoracic exploration while the cancer is within bounds and often before tissue diagnosis has been made. Resection has cured approximately one-half of the patients whose carcinoma was localized to the lung at the time of exploration. Cure may be possible in even a greater proportion of asymptomatic patients whose roentgen survey lesion is resected within a few weeks of detection. Responsibility for early apprehension of both silent and asymptomatic neoplasms must be shared by physician and surgeon alike. Success depends upon the prompt appraisal of cancer potential in an abnormal shadow regardless of the circumstances which lead to its discovery.

Evaluation of the patient requires one or more of five steps: (1) Adequate radiology in order to check the presence of the discovery shadow and establish the existence of a cancer potential, and for localization; (2) search for irreversible poor general physical state or incurable associated disease; (3) search for distant metastases; (4) bronchoscopic assurance that trachea and bronchus to the uninvolved side are sound; (5) exploratory thoracotomy.

In twenty years more than 1,100 patients with primary pulmonary carcinoma referred to the Overholt Thoracic Clinic have had their diagnosis verified histologically. An analysis of various groups from this experience will serve as a basis for comment. Patients are seeking advice sooner now than a few years ago. Chest films are obtained with less delay. More abnormal shadows are being discovered in asymptomatic individuals. Efforts at palliation are beginning to yield benefits. Five-year cures are constantly being added to the list of survivors.

ROENTGENOLOGY

The x-ray is the most valuable and dependable instrument with which to demonstrate abnormal densities situated within lung tissue. It is the only practical way to screen for silent cancer. Fortunately the mechanics of screening the lung are far simpler than of screening any other region, including skin, breast, buccal cavity or female genital tract. All negative cases can be eliminated without the doctor's even seeing the patient. Technicians can collect the evidence, and only the small percentage of patients showing abnormal findings require a time-consuming examination.

Many cancer suspects are being found in mass surveys for tuberculosis. However, most of these surveys are single-purpose programs. To give adequate protection the screening should be an annual affair in all persons past forty years of age. The interval should be shortened to four months in the most susceptible group—men of cancer age who smoke.

Such a screening program can be implemented by individual patient-doctor arrangement. All existing facilities for taking standard or miniature films should be made available for screening purposes. Single films, taken and developed by technicians on a mass production basis, can keep the cost as low as that of a urinalysis or blood count. Every doctor should make it his responsibility to see that his patients have this protection.

An abnormal shadow detected, however, is not a lesion diagnosed. X-ray, unassisted, cannot make the diagnosis. The protean x-ray manifestations of pulmonary carcinoma are determined by several factors such as: (1) location, (2) extent, (3) degree of bronchial occlusion, (4) associated infection and (5) vascular or lymphatic involvement.

The shadows of cancer simulate those of

many other conditions. The most common are: tuberculosis, pneumonia and pneumonitis of all types, lung abscess and bronchiectasis.

Complete x-ray study must establish that the abnormal intrathoracic x-ray shadow is bona fide and not a phantom shadow or misinterpretation of a normal anatomic variation. Usually posterior-anterior and oblique or lateral exposures combined with fluoroscopy are sufficient for this purpose. Occasionally, stereoscopic exposure, tomography, Bucky grid or over-exposed films give assistance. Very rarely, if ever, is there need to detail x-ray diagnosis with bronchogram, pneumothorax or pneumoperitoneum.

X-ray shadows containing calcium in old, healed lesions are common findings. Calcium distributed evenly throughout an abnormal shadow weighs heavily against malignancy. If a calcific deposit has a second component or satellite shadows which are entirely free of calcium, malignancy cannot be ruled out with certainty.

The exact malignant potential of lesions producing abnormal shadows cannot be determined. Hood et al.[1] stated that bronchogenic carcinoma was found in 16 per cent of 156 resected solitary circumscribed x-ray lesions of the lung. Grow, Bradford and Mahon[2] found malignant 19 per cent of eighty-six circumscribed lesions undiagnosed prior to exploration. Abeles and Ehrlich[3] found one-third of twenty-one lesions explored to be malignant. Harrington[4] explored fifty-two patients with asymptomatic intrathoracic lesions and found 31 per cent malignant. O'Brien, Tuttle, and Ferkaney[5] reported a series of pulmonary "coin" lesions containing 43 per cent malignancies. Sharp and Kinsella[6] reported 22 per cent malignancy in their experience with the "isolated pulmonary nodule." Fink[7] found 33 per cent malignant. At the Overholt Thoracic Clinic 18 per cent of 268 abnormal intrathoracic x-ray shadows discovered on chest roentgenographic screening were found to be malignant lesions at exploration. Although these series are not comparable, an absolute figure for the cancer potential of unexplained densities in the lung is not necessary. It is important to remember that some change in density caused the shadow, and that a significant number are cancerous densities. If the cancer potential is ever considered to be more than 1 per cent, it is safer to explore than to wait and see, since the risk of exploration is less than 1 per cent.

ADJUNCTS TO DIAGNOSIS

Cytologic examination of sputum or bronchial secretions by experienced personnel is a valuable adjunct to the diagnosis of pulmonary carcinoma, provided negative reports are not permitted to delay exploration. At the New England Deaconess Hospital negative cytology has been reported preoperatively in nearly one-fourth of all histologically verified pulmonary cancers. Furthermore, benign lesions have yielded 2 per cent positive reports, and an additional 8 per cent have been reported suspicious of malignancy.

Aspiration biopsy through the chest wall is rarely used and is unwise and unnecessary in most instances. It has value when a peripheral tumor exists and when (1) peripheral metastases are not accessible for biopsy; (2) tumor cells cannot be demonstrated in sputum or in secretions obtained by bronchial aspiration; (3) the tumor is inaccessible or too vascular for bronchoscopic biopsy; (4) the general condition is too precarious to permit exploration. It must be remembered that the specimen obtained through a needle is not always adequate for complete histologic diagnosis, and there is always the real risk of tumor implantation along the track of the puncture.

GENERAL ASSESSMENT

The primary purpose of the history and physical examination should be a painstaking evaluation of the general physical state and a meticulous search for distant metastases. Over 90 per cent of all our symptomatic cases reported either cough, chest discomfort, hemoptysis, arthritis, weight loss, fatigue, change in character of breathing, or combinations of these disturbances. Such symptoms may be present with either localized or advanced disease and do not furnish a reliable guide as to curability. Abnormal physical findings such as fever, marginal pulmonary reserve, consolidation, emphysema, or even fluid free of tumor cells do not necessarily spell out hopelessness.

Irreversible precarious general health prompted rejection of thoracotomy for only twenty-eight cases (3 per cent) of 884 studied by us between 1941 and 1953. Surgery was

refused for persistent decompensated cardiac valvular disease—especially aortic, persistently decompensated myocardium, terminal cachexia, active widespread pulmonary tuberculosis, severe pulmonary fibrosis and emphysema, associated incurable proved lymphosarcoma, suggestive evidence for distant metastases—recent psychosis and jaundice.

Proved distant metastases contraindicated thoracotomy in 226 (26 per cent) of the 884 cases. Supraclavicular lymph node biopsy was always performed if there was a suggestion of lymph node enlargement in that area. Accessible metastatic lesions were histologically verified. Exceptions were made when there were multiple neurologic or bone lesions or gross superior mediastinal venous obstruction. Solitary bone lesions may represent benign disease and should be biopsied. The more common sites of distant metastases were supraclavicular lymph nodes, brain, liver, axial and peripheral skeleton, and axillary lymph nodes. Pleural fluid is not an absolute contraindication to surgery unless it contains tumor cells. Vocal cord paralysis on the side of tumor is a grave sign and usually contraindicates exploration, especially if associated with pleural fluid, widened mediastinal x-ray shadow or superior mediastinal obstruction.

Since paralysis of the diaphragm can occur as the result of inflammatory disease of the lung or without any discernible intrathoracic pathologic disorder, it does not preclude resectability. On occasion, patients with extensive disease and only presumptive evidence of distant spread have had a lobe or a lung removed with worth while palliation. This has been especially helpful in patients with violent coughing spells, chest discomfort, arthritic pain or other manifestations of toxicity.

BRONCHOSCOPY

Bronchoscopy has its greatest value in determining technical resectability, not in obtaining biopsy. When careful physical examination and investigation of suspicious peripheral lesions have failed to contraindicate exploration, bronchoscopy becomes the next logical step in the patient's preoperative evaluation. It is the most precise gauge of the tumor's extent within the major air passages. Contralateral bronchial or tracheal involvement are findings which make resection either impossible or hazardous.

Fixation of the mediastinum suggests neoplastic invasion of the mediastinal lymphatic system and is the prognostic analogue of "frozen pelvis" in carcinoma of the cervix uteri. Mobility of the tracheobronchial tree can be determined with gentle pressure transmitted through the tip of the bronchoscope.

TABLE 1
HISTOLOGIC VERIFICATION (CONSECUTIVE CASES OF PRIMARY CARCINOMA OF LUNG)

Method	1932–1940 99 Cases (%)	January, 1949–September, 1953 462 Cases (%)
Bronchoscopy biopsy	66	22
Exploration and biopsy	18	57
Biopsy metastasis	7	11
Necropsy	5	2
Pleural fluid cytology	3	2
Sputum cytology without exploration	0	6

Hard fixation usually means carcinomatous invasion of the paratracheal lymph nodes, but, as in the pelvis, inflammation can produce immobility. To deny exploration because of this finding alone is unfair to the patient.

Enlargement of mediastinal nodes may indent the trachea or major bronchi and cause rounding of the normally sharp carinal spur. These findings most often are associated with lymphatic spread but quite often represent only non-specific inflammation. Although direct invasion of most types of tumor into trachea or contralateral bronchus is an absolute contraindication to successful resection, mediastinal fixation and enlargement of the hilar and mediastinal lymph nodes is but a presumptive contraindication.

Unnecessary diagnostic bronchoscopy, with its delay of weeks or months, may rob the patient of an opportunity for cure. In addition to avoidance of bronchoscopic delay, there should be also an elimination of extended serial x-ray studies, protracted antibacterial therapy and tuberculosis investigation with time-consuming laboratory studies such as guinea pig inoculation or cultures.

With emphasis on a more direct and positive

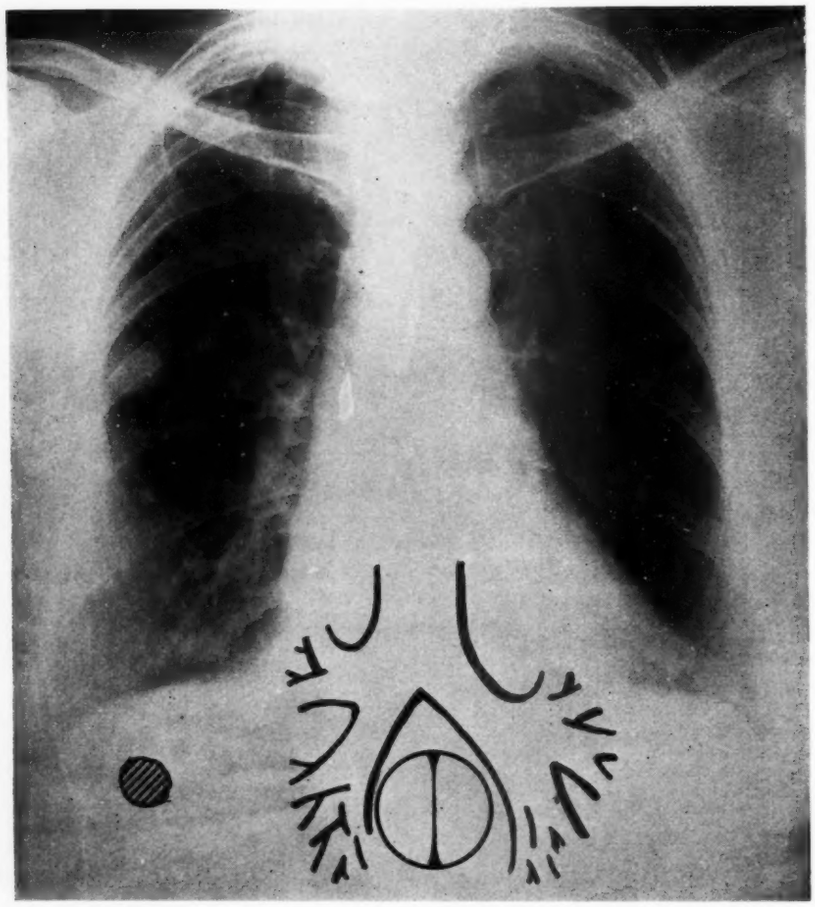

FIG. 1. Mrs. S. R., age fifty-four. The decision to explore was made on the basis of x-ray evidence. The patient was asymptomatic. The discovery film five months previously revealed an abnormal density of similar size and character. In this instance, as suspected, bronchoscopy was negative. The insert depicts the space relationship between the lesion and the range of bronchoscopic vision. Within the circle the fine straight line represents a normally sharp carina. In order to save discomfort, time and expense, bronchoscopy was performed in the two minutes preceding the insertion of an intratracheal tube for anesthesia. Right pneumonectomy for circumscribed, poorly differentiated adenocarcinoma was performed on December 20, 1949. The convalescence was uneventful. Total hospital stay was twenty days. She is well now, four and a half years later.

diagnostic and treatment program our clinic has seen a fall in its bronchoscopy-histologic verification from 66 per cent prior to 1941 to 22 per cent since 1949. (Table 1.) A concomitant rise in verification at exploratory thoracotomy from 18 per cent to 57 per cent mirrors the philosophy that suspicious roentgen shadows must be explored before prolonged and expensive diagnostic or quasidiagnostic procedures have spent the patient's last hope for cure.

In a group of 462 cases of verified primary pulmonary carcinoma, 348 bronchoscopies were performed and 104 bronchoscopies with pathologic diagnosis were achieved. Thus, although 76 per cent of all patients were bronchoscoped and 30 per cent of the bronchoscopies gave a biopsy positive for malignancy, only 22 per cent of all the patients had their diagnosis verified preoperatively by this means. Since 74 per cent of the lesions in this group of patients were centrally placed near the hilum, the statistics suggest a failure of bronchoscopy to discover cancer accessible in the proximal bronchi. Clarification of these statistics rests chiefly with three facts:

1. Many of the lesions centrally placed had obvious distant metastases, and histologic

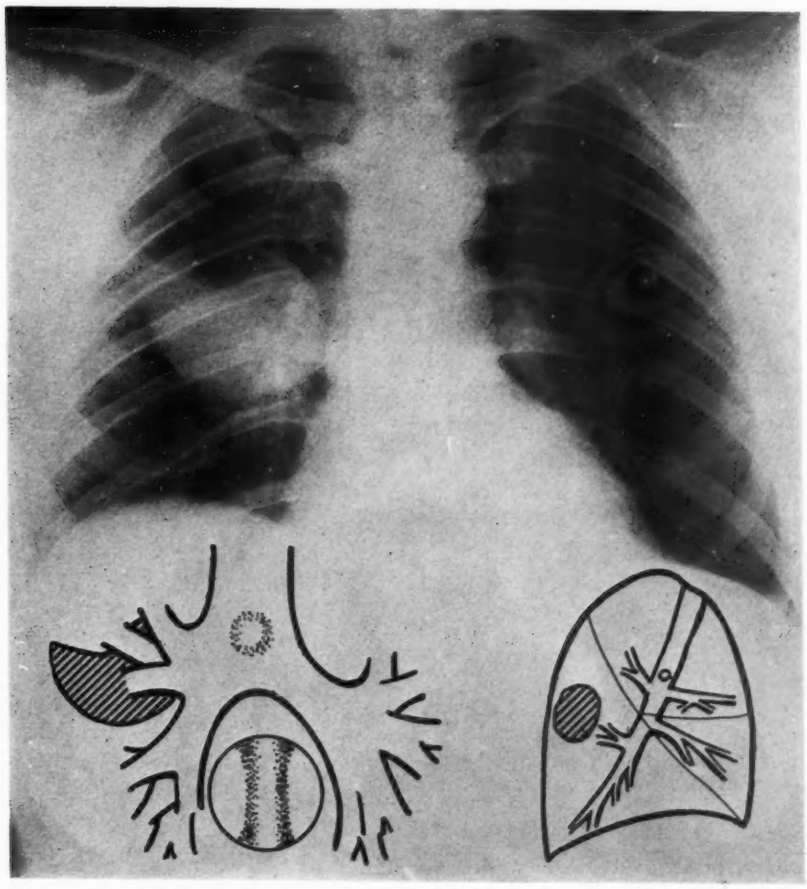

FIG. 2. Mr. A. C., age forty-seven. The decision to explore was made on the basis of the x-ray evidence. The only significant symptom was hemoptysis of ten days' duration. Discovery film (survey) two months previously when patient was asymptomatic revealed a slightly smaller shadow. Lateral projection (see insert right) placed the lesion in the superior segment of the lower lobe. It was posterior and out of bronchoscopic range. Since resection was indicated, the exploration was planned to follow the bronchoscopy immediately. The essential bronchoscopic findings are indicated in the insert (left). The appearance of the blunted and widened carina is shown in the circle. Slightly above the carina and in the membranous portion of the trachea, there was a bulge suggestive of an enlarged mediastinal node. As suspected, all bronchial airways within bronchoscopic view were open. Upon exploration, February 3, 1949, grade III epidermoid carcinoma was found. Twenty-four lymph nodes, some tremendously enlarged, were removed. All were negative for tumor. Right pneumonectomy was followed by a satisfactory convalescence. The total hospital stay was ten days. Now, five and a half years later, the patient is living, well and working as a plumber.

verification came from those sources rather than from bronchoscopy.

2. A recent practice at the clinic has been to omit biopsy in those patients who are to undergo immediate thoracotomy and have uninvolved trachea, carina and contralateral bronchus. It is not always wise to remove a specimen via the bronchoscope when a lesion is visible. Serious intrabronchial hemorrhage is not a rare occurrence. Its risk should be weighed against the theoretic advantage of preoperative histologic verification.

3. Some carcinomas can be seen in the upper lobe bronchi with right angle telescopic lenses but are not within reach of the biopsy forceps.

The best interests of the operable patient are served when there is the least possible delay between bronchoscopy and thoracotomy. X-ray evidence alone forces the issue of exploration in all early cases. Unless the odds

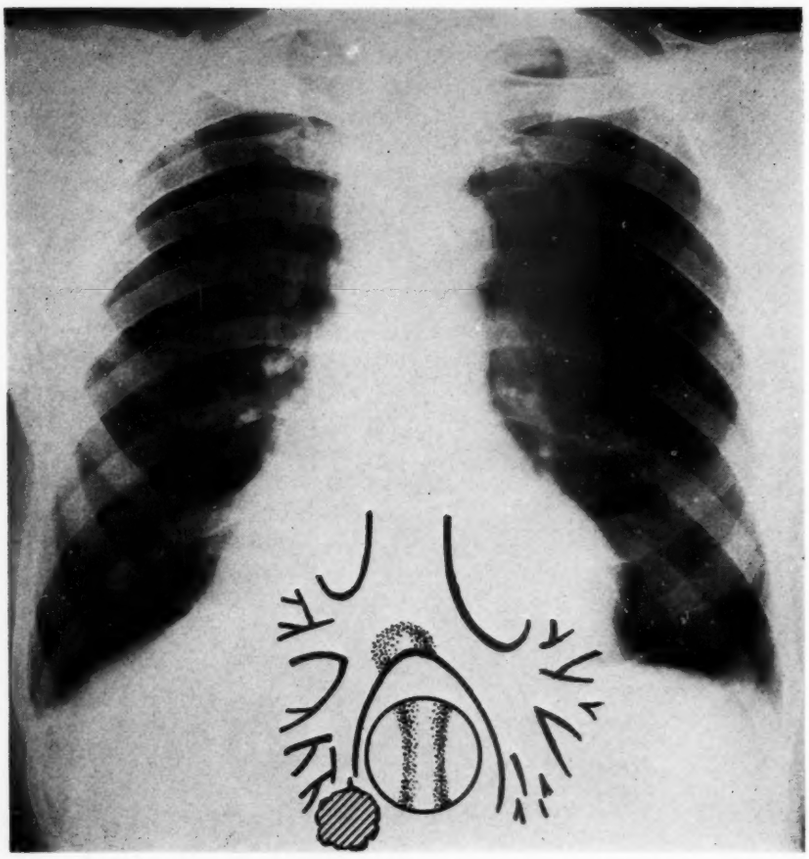

FIG. 3. Mr. J. G., age seventy. The decision to explore was based upon the x-ray evidence. A chronic cough was present for eighteen months and hemoptysis for two weeks. His general physical condition was satisfactory. There was no evidence of distant metastases. He was toxic and resection was desirable regardless of mediastinal lymph node involvement. Since bronchoscopy failed to demonstrate a tumor above a safe level for bronchial division, exploration followed immediately. The insert indicates the findings at bronchoscopy. The carina was wide. A bulge was seen in the posterior wall of the trachea just above the carina. A fungating mass projected into the lower lobe bronchus, and purulent secretions welled up around it. On October 19, 1948, right pneumonectomy was performed for a grade III epidermoid carcinoma. The medial half of the lower lobe was indurated and airless. All visible lymph nodes, eleven in number, were resected. Some were very large and firm. All were negative for tumor. The convalescence was uneventful and the total hospital stay was twenty-four days. His physician reports now, nearly six years later, that the patient is alive and well.

strongly suggest tracheal involvement and a frozen mediastinum, the patient might as well be scheduled for preoperative bronchoscopy under topical anesthesia with the plan to proceed immediately (i.e., the same hour) with thoracotomy, should no unexpected contraindication be discovered. Fore-oblique and right angle telescopic lenses introduced through the bronchoscope assist in the thorough examination of the tracheobronchial system. In silent cancer and in most early symptomatic cancer the bronchoscopy will be negative. However, a neoplasm may be seen involving the primary or secondary bronchi, and be accessible for safe biopsy. (Figs. 1 to 3.)

Doubtfully resectable cases are scheduled for separate bronchoscopic evaluation so that the patient and operating room personnel will be spared a cancellation. It is our practice to explore the cervical area and upper mediastinum whenever there is a question of resectability. This often is done as an office procedure. In many cases it is a simpler method of settling the issue than bronchoscopy. (Fig. 4.)

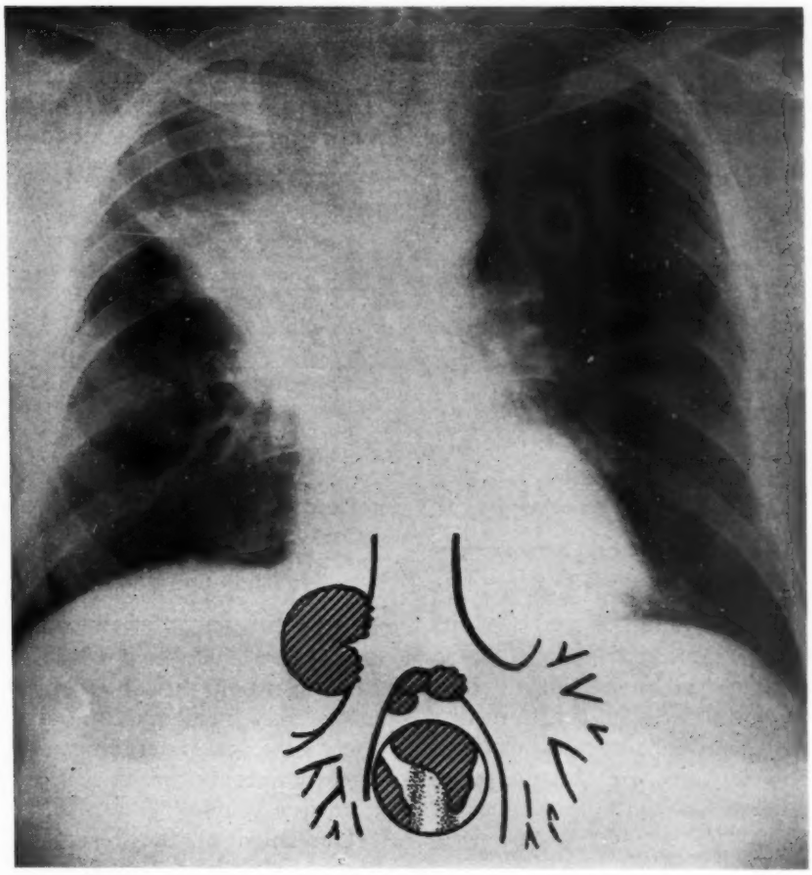

FIG. 4. Mr. A. S., age fifty-four. The decision to explore could not be made on the x-ray evidence alone. Pronchoscopic information was essential before a decision regarding therapy could be made. He had been treated for three attacks of "virus pneumonia" over a nine-month period. There was fever, cough, hemoptysis and a weight loss of 30 pounds. There was no peripheral lymphadenopathy. Upon bronchoscopy in March, 1951, the carina and right main bronchus were grossly involved by tumor tissue which was friable and bled easily. The right upper lobe orifice was occluded by extrinsic pressure. The lower trachea and main bronchi were fixed. Use of the biopsy forceps was deemed unwise because risk of hemorrhage was great. Secretions and sputum were both positive for tumor cells. The patient was advised that surgery was not indicated. No therapy was given. Total hospital stay was two days. He succumbed twelve months later.

EXPLORATORY THORACOTOMY

Exploratory thoracotomy is the final arbiter for many as to resectability. It gives a rapid diagnosis when that diagnosis is urgently needed. It evaluates more accurately than any other means the extent and histologic type of the growth. The thoracic surgeon has an advantage over the abdominal surgeon. Vision is not hampered at thoracotomy by an obtrusion of multiple mobile organs. The surgeon's fingers more easily detect a lesion in the delicate airy substance of the lung than in a solid structure such as the liver or kidney. Palpation of lung tissue is more precise than the handling of slithering coils of intestine. Tests of inflation and deflation of the lung may yield additional evidence of abnormality. Nodes in the direct lymphway of the disease-bearing segment can be directly approached. Parenchymal lesions can be totally removed for biopsy by wedge, segmental or lobar resection.

Although accuracy in diagnosis and evaluation demands a wider use of exploration, reasonable safety of the procedure must be assured. Fortunately, advances in surgical technics have brought operative mortality in cases of pul-

monary carcinoma explored, biopsied and closed without resection because of massive mediastinal invasion to slightly more than 1 per cent. Exploratory thoracotomy for benign disease is well below one-half of 1 per cent. (Table II.)

TABLE II
OPERATIVE MORTALITY IN CARCINOMA

Years	Exploration only (%)	Resection of Localized Lesions (%)
1933–1940	28	33
1941–1945	12	7.7
1946–1950	8.5	13
1951–1953	1.3	2.7

With the safety, accuracy and necessity of exploratory thoracotomy well established its use has become more frequent in our clinic. In the past four years 71 per cent of all cases seen have been explored. This high rate results partially from the fact that some preselection has been made by referring physicians. Also,

TABLE III
HISTOLOGICALLY VERIFIED PRIMARY PULMONARY CARCINOMA

Year	Thoracotomy (%)	Resection (%)
1933–1940	43	18
1941–1945	63	30
1946–1950	67	42
1951–1953	71	49

extension of surgical palliation to more patients has raised the exploration rate. It is significant, moreover, that the resectability rate has risen three times as rapidly as has the exploration rate. (Table III.)

RESECTION

Early exploration has had a large part in making safe resection possible in an increasing number of cases. Resection has been performed on nearly two-thirds of all patients explored for lung malignancy since 1945. Operative mortality, including all deaths occurring within a month after operation, has fallen steadily. In the last three years the over-all mortality rate was 7 per cent; for localized lesions the rate was 2.7 per cent.

Two-thirds of the pulmonary resections from 1941 to 1949 were for lesions which had evidence for extension outside the lung to the mediastinum or chest wall. Some of the resections were performed with the hope of palliation; in others, histology revealed unsuspected metastases in mediastinal lymph nodes. Of all these patients undergoing resections for lesions already outside the lung, 9 per cent lived more than five years.

TABLE IV
POSTOPERATIVE RESULTS THIRTY-SIX LUNG CANCERS DISCOVERED BY X-RAY SURVEY

Localized to Lung (22)	Extended beyond Lung (14)
16 Survivors: 8—One to three years 8—Three years or more	3 Survivors: 2—One to three years 1—Three years or more
6 Dead: 3—Of disease 2—At operation 1—No follow-up	11 Dead: All presumably of disease

One-third of the resections were in cases without evidence of extension beyond the lung. From this group one of every four lived five years or more.

Thirty-six resections were performed for cancers discovered during radiologic screening. Of those resected, nineteen (53 per cent) are alive more than one year; nine (25 per cent) are alive more than three years. Twenty-two of the thirty-six resections (61 per cent) were in lesions localized to the lung. From this favorable group sixteen (73 per cent) are alive more than one year; eight (36 per cent) are alive more than three years. One-half of all patients in the survey groups presented themselves for therapy more than seven months after the original x-ray had been found "suspicious for tumor." This delay was caused in part by the reluctance of patients and in part by physicians in quest of definite diagnosis prior to suggesting thoracotomy. Of all the patients coming to resection within two months of the first x-ray, two of three are alive more than one year. Of all patients still asymptomatic at the time of surgery, three of four are alive more than one year. Of asymptomatic patients resected within two months of survey,

nine of ten have survived one year or longer. (Table IV.)

Safer resection has given dividends in prolonged life, relief of symptoms and cure. The earlier, silent cases have had the least risk from operation, and they have benefited most in cure.

SUMMARY AND CONCLUSIONS

1. The abnormal shadow by x-ray is evidence enough to demand exploration in many instances.

2. The cancer potential of such shadows has been discussed.

3. Each cancer patient deserves proper evaluation as to resectability. A differentiation must be made between absolute and presumptive evidence of extension of the primary growth beyond surgical limits.

4. Discomfort, time and expense can be saved for those patients who probably should be explored, regardless of negative or positive bronchoscopic findings, by carrying out bronchoscopy as a preliminary to intratracheal intubation and exploration.

5. Millions upon millions of chests are being examined by x-ray each year. More shadows that carry a cancer potential are being recorded. A growing proportion of patients with pulmonary cancer are resectable. More people are being cured.

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The Surgical Treatment of Carcinoma of the Lung

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IN any discussion on pulmonary diseases the subject of cancer of the lung will be of prime importance. This is true because of the extraordinary increase in the incidence of cancer of the lung in the past two decades. It has become the most common cancer in white males, exceeding even cancer of the stomach. The increased death rate from this disease among the male population in this country is illustrated in Figure 1. The same rising death rate did not occur in women. (Fig. 1.) This remarkable increase in the deaths from cancer of a particular organ in men has aroused much speculation. Prominent among the theories which have been advanced to explain the increase is the theory that prolonged and heavy cigarette smoking has been a significant contributing etiologic factor in the most common form of this cancer, namely the squamous cell type. The most recent extensive statistical study of this relationship was published by Hammond and Horn.[9]

The following remarks concerning the surgical treatment of cancer of the lung are based upon a consecutive series of 617 patients seen by the senior author, his associates Drs. Allbritten and Templeton, and the resident surgical staff at the Jefferson Medical Center. These cases were studied between April 1, 1946, and January 1, 1954, and 441 of the patients were operated upon. The remaining patients were not explored because of obvious evidence of metastasis outside the involved hemithorax.

The symptoms of carcinoma of the lung have been adequately described in numerous articles in recent years and will not be considered here. In 98 per cent of the patients in our series there was a detectable abnormality in the x-ray film of the chest and in 85 per cent a presumptive diagnosis of cancer of the lung was made by x-ray. By means of bronchoscopy, a positive histologic diagnosis was established in 65 per cent of our cases; in 23 per cent by biopsy, and in an additional 42 per cent by cytologic examination of bronchial secretions. This means that in 23 per cent of patients, the lesion was in one of the main bronchi or in the upper portion of a lower lobe bronchus, or projecting into a main bronchus from the orifices of the upper lobe or middle lobe bronchi. However, in 42 per cent of the group, when a biopsy was unobtainable, a positive histologic diagnosis was made by aspiration of the bronchial secretions from the suspected lobar bronchus. In the remaining 35 per cent, a histologic diagnosis was not obtained preoperatively and the patients were explored promptly on the basis of x-ray findings and history. At the time of exploration, a radical operation was not performed until a positive histologic diagnosis was established by examination of a frozen section of tissue.

Needle biopsy through the chest wall, in any patient in whom the lesion might be operable, is mentioned only to be condemned. It is, of course, justifiable to establish a histologic diagnosis in this fashion if it is obvious that the lesion is inoperable. In one of our patients a needle biopsy had been performed at another institution. The lesion proved to be operable and pneumonectomy was performed. Some months postoperatively a nodule of cancer appeared in the needle tract.

The treatment of cancer of the lung, where there is no evidence of distant metastasis, is the complete surgical extirpation of the cancer with en bloc removal of all mediastinal lymph nodes. In our experience such surgical treatment has resulted in a five-year survival rate of 26 per cent of all the patients in whom it was possible to remove the cancer of the lung. In sharp contrast to this is the fact that 99 per cent of all the patients in our series in whom it was

not possible to remove the cancer were dead within eighteen months following the establishment of the diagnosis, 92 per cent being dead within twelve months. Thus of the 379 patients in whom the cancer was not removed, only three are alive more than eighteen months after establishment of the diagnosis. In these three patients, the diagnosis was made on cytologic examination of the bronchial secretions. Despite the absence of histologic section of the tumor we believe that the diagnosis of cancer of the lung in these patients is correct.

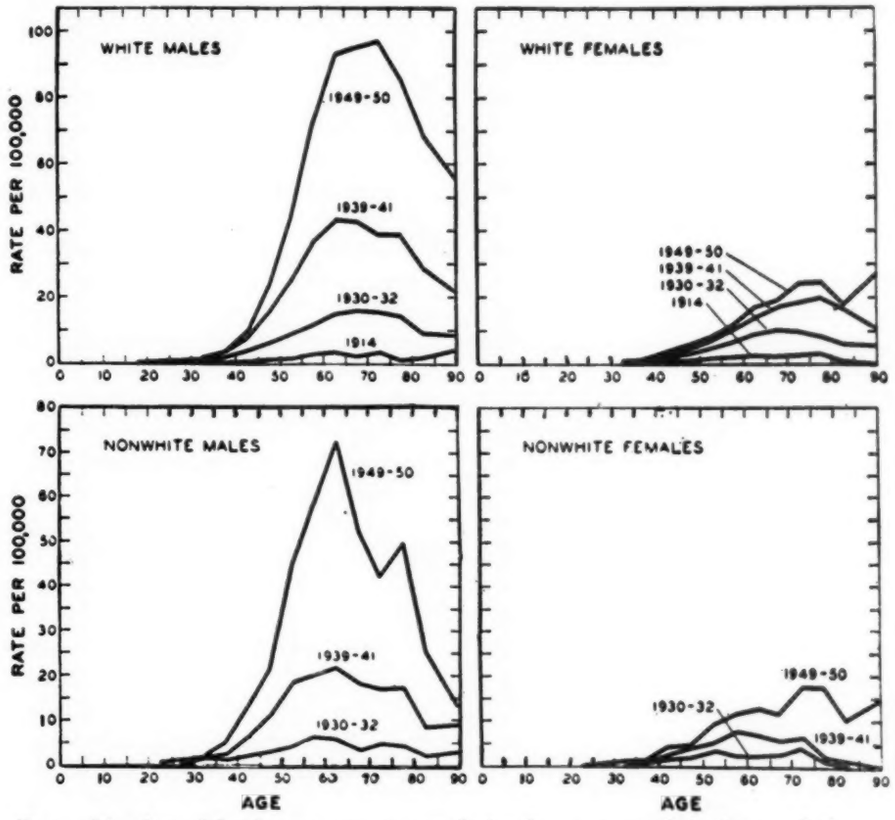

FIG. 1. Number of deaths per 100,000 population from cancer of the lung and pleura. The striking increase in death rate of males between the 1930–1932 period and 1949–1950 period is apparent. (Reproduced from *Industrial Med. & Surg.*, 23: 253–257, 1954, with permission of the author and publisher.)

OPERABILITY

If there is any evidence of cancer outside the involved hemithorax, the patient should not be operated upon. The most common site of metastasis outside the involved hemithorax is to the cervical lymph nodes on the ipsilateral side. The axillary lymph nodes on the same side are much less commonly involved. In patients dying of cancer of the lung, about 40 per cent show metastasis to the liver and to the adrenals at autopsy.[5] Metastasis to bone, pancreas and kidney are somewhat less frequent. Even less frequent, but constituting a significant proportion, is metastasis to the brain, to the opposite lung, and to skin or subcutaneous tissues.[5,8] Fortunately the most common earliest site of metastasis is to the cervical lymph nodes, which are frequently palpable. Any enlarged cervical lymph node should therefore be removed and examined histologically.

Invasion of the ribs and intercostal muscles by a peripherally located pulmonary cancer is a bad prognostic sign. Even though it is possible to remove the involved portion of these structures en bloc with the lung, such patients in our experience have not survived more than eighteen months. Peripheral lesions in the lung with pain radiating around the chest, or localized to the region of the tumor, have frequently invaded the chest wall. Paralysis of the phrenic nerve is not regarded as a contraindication to operation. This nerve is

usually infiltrated by a hilar growth which extends into the pericardium. It is, of course, quite easy to remove the involved nerve and pericardium if the lesion is otherwise operable. On the other hand, paralysis of the left recurrent laryngeal nerve has invariably in our experience, indicated an unresectable growth. In these patients the carcinoma generally originates in the left main bronchus, or in the left upper lobe. We have explored twenty-two such patients and in all it was impossible to remove the growth because of extension into the wall of the aorta or massive invasion of the mediastinum. The right recurrent laryngeal nerve, of course, is only rarely involved because of its high position in the right side of the thorax. Growths originating in the apex of the lungs producing Pancoast's syndrome have also proved to be unresectable.

A pleural effusion, especially when bloody, is also a bad prognostic sign. If the centrifuged sediment of such fluid contains cancer cells, the patient is not explored because pleural metastasis will be widespread. We have as yet been unable to perform a total pleurectomy together with a radical pneumonectomy. If no tumor cells are found in the centrifuged sediment, the patient should be explored, particularly if the histologic diagnosis has not been established. We operated upon one patient who had a massive, bloody, pleural effusion, who was thought to have an inoperable cancer, but in whom no histologic diagnosis had been established. The patient was found to have a massive hemothorax of undetermined etiology with a completely atelectatic lung. The hemothorax was evacuated, the thickened visceral pleura was peeled off the surface of the lung allowing complete re-expansion. The patient is symptom free two years after operation with no signs of carcinoma.

EXTENT OF THE OPERATION

No extensive study of the pattern of metastasis to pulmonary and mediastinal lymph nodes has been made in cancer of the lung comparable to those made by Gilchrist and David[7] in cancer of the colon and by Coller, Kay and McIntyre[4] in cancer of the stomach. Such a study was begun in our laboratory several years ago, but was never carried to completion. The lungs were cleared by Gilchrist's technic and all lymph nodes were removed, labeled and examined histologically. The results of this study, together with observations at operation on more than 400 patients with cancer of the lung, have enabled us to reach some tentative conclusions concerning pathways of lymphatic spread. In general, cancers of the upper lobe are prone to metastasize to the tracheal lymph nodes, whereas those of the lower lobes tend to metastasize to the carinal group of lymph nodes. The intercommunications between lymph nodes around the lobar bronchi and the main bronchi are such that we are convinced that it is impossible to perform an ideal cancer operation by doing a lobectomy. In small, peripheral tumors wide excision of the tumor will prove as "curative" as either lobectomy or pneumonectomy provided that metastasis has not occurred. However, it is obviously impossible for the surgeon to be sure that lymph nodes are not already involved. Therefore, radical pneumonectomy should be performed on all patients with cancer of the lung no matter what the size of the initial growth or its location, and regardless of whether or not there appears to be metastasis to nodes. Our only exception to this rule of performing a radical pneumonectomy has been in those patients who require extensive excision of the chest wall because of involvement by the cancer. In these patients we usually perform lobectomy or bilobectomy rather than pneumonectomy because of the forbidding mortality when pneumonectomy is performed in conjunction with extensive resection of the chest wall. Furthermore, the prognosis in such cases is, at best, extremely poor.

PREOPERATIVE PREPARATION

Anemia, if present, should be corrected by blood transfusion prior to operation. If there is a weight loss of 15 pounds or more, the patient is also given at least 500 ml. of blood preoperatively, even though the hematocrit and hemoglobin are within normal limits. In our experience such patients with considerable weight loss invariably have a diminished circulating blood volume. Only incipient, or actual heart failure, or such extensive pulmonary emphysema that the patient is dyspneic at rest, are regarded as contraindications to pneumonectomy. If there is an infection of the lung distal to a bronchus obstructed by the tumor, antibiotics are employed preoperatively. In most patients this will control the infection. In an occasional patient the fever will not

subside until the infected lung is removed. We have had a number of patients in whom pulmonary tuberculosis was coexistent with cancer of the lung. If there is active tuberculosis in the lung contralateral to the cancer, operation is of course contraindicated.

ANESTHESIA

An intratracheal tube with an inflatable cuff should always be used. It ensures an airway and permits the easy aspiration of secretions during the operation. The inflated cuff allows adequate ventilation of the lungs and avoids gastric distention with the anesthetic gases. In several thousand intrathoracic operations we have seen no ill effects from using such balloons.

The intubation is performed after local anesthetization of the pharynx and larynx with 0.5 per cent pontocaine or, in patients who are nervous and apprehensive, after the induction of anesthesia with intravenous sodium pentothal® and nitrous oxide and oxygen. Once the intratracheal tube is in place and the cuff inflated, anesthesia is continued and maintained with a mixture of ether and oxygen.

The patient is placed on the operating table in the lateral position, with the diseased side uppermost. We realize that this position increases the difficulty of providing adequate pulmonary ventilation during the operation. However, it gives the best exposure, through a posterolateral incision, for a difficult pneumonectomy. Neither the prone nor supine positions provide the same excellent access to all parts of the opened hemithorax. With the aid of a mechanical ventilator, which provides negative pressure during the phase of expiration, we have been able to maintain an adequate pulmonary ventilation during prolonged and difficult pneumonectomies, even when there was severe emphysema of the contralateral lung. Furthermore, it has not been necessary to use a curare-like drug in order to have a completely quiet diaphragm. The carbon dioxide tension falls, and the pH rises, sufficiently so that no diaphragmatic activity occurs even with a very light plane of anesthesia.

The tracheobronchial tree must be kept at all times free of secretions, mucus and pus. Aspiration of the trachea is repeated as often as necessary throughout the course of the operation. It is routinely done when the patient is turned on his side before the chest is opened and is repeated as soon as the pleural cavity is entered. The necessity for such aspiration must also be borne in mind when the diseased lung is being handled or compressed. If there are abundant secretions from the diseased lung entering the trachea and the opposite bronchus, the bronchus of the diseased side should be rapidly closed with a clamp or by tying a heavy tape around it at the start of the operation. The last aspiration is performed as the intratracheal tube is being withdrawn, after deflation of the cuff, at the conclusion of the operation when the patient is placed in the supine position on the bed or stretcher to leave the operating room. The final consideration of importance with regard to anesthesia is that the plane should be light throughout the operation. There is no necessity for the muscular relaxation which is required in so many abdominal operations. We make it a practice to have the patient so light that when the skin stitches are being inserted, the patient moves because of the stimulus from the needleprick in the skin. Usually the patient is able to arouse sufficiently to respond to questioning before he leaves the operating room.

TECHNIC OF RADICAL PNEUMONECTOMY

Many authors have made contributions to the development of the technic of radical pneumonectomy in recent years.[1,6,10,12] Brock,[2] Cahan[3] and Higginson[11] have especially stressed block dissection of lymph nodes. Later we will describe the technic we have been using for the past five or six years. Four or five scratches are made in the skin at right angles to the line of the proposed incision. Such scratches are of aid in the accurate closure of the long, curved wound. The skin incision is begun at the level of the spine of the scapula starting at a point one-third of the distance from the dorsal border of the scapula to the spines of the vertebra. The incision is carried downward and forward close to the dorsal border of the scapula passing just below the inferior angle of the scapula and extending forward as far as the fifth or sixth costal cartilage. (Figs. 2 and 5.) The latissimus dorsi muscle is completely divided in the line of the incision. The lower fibers of the trapezius muscle are divided for a distance of about 6 cm. It may or may not be necessary to divide some of the lower fibers of the rhomboideus major muscle. The lowermost fibers of the serratus magnus muscle are divided up to the fifth or sixth rib. At this level, they are split

in the direction of their fibers over the rib to be removed as far as the costal cartilage.

Removal of either the fifth or sixth rib gives adequate exposure for a radical pneumonectomy. Frequently the fifth rib is removed when the cancer is in the upper lobe and the sixth rib if there is a bulky tumor in the lower lobe. The rib is removed subperiosteally from the angle posteriorly to the costal cartilage in front. The posterior layer of the periosteum is then incised and the pleural cavity opened. Adhesions between the parietal and visceral pleura, if present, are sufficiently separated so that the lung may be depressed with a broad malleable retractor covered with a gauze sponge. This retraction of the posterior portion of the lung enables the remaining posterior segment of the rib to be excised from within the chest from the point of previous division to the transverse process of the vertebra. The pleura and posterior layer of periosteum overlying this rib segment is incised with a scalpel and the periosteum is completely stripped from the rib down to the transverse process. The rib is again divided here with large rongeur forceps. During the resection of this posterior segment of the rib, no retraction of the erector spinae mass is made, nor are any of the fibers of the muscle divided. This method of removing the posterior segment of the rib without disturbing the overlying erector spinae muscle aids greatly in obtaining an air tight closure of the posterior portion of the wound after completion of the pneumonectomy. A self-retaining rib spreader is then put in position, protecting the wound edges with gauze sponges. Opening the rib spreader to its fullest extent should be done slowly so as to allow tissues to stretch. With this precaution, fractures of the ribs above and below the wound can be avoided.

With the thorax widely opened, the first step in the operation is adequate exploration in order to determine whether the lesion can be extirpated. If the tumor is peripheral and has invaded one or more ribs and intercostal muscle bundles, the feasibility of excising these structures together with the involved lobe of the lung should be determined. As stated previously, lobectomy, rather than pneumonectomy, is advisable in these patients. In the usual case all adhesions between the lung, the wall of the chest, the diaphragm and mediastinum should be separated. Until this is done, it is often impossible to determine the feasibility of a radical pneumonectomy. If a positive histologic diagnosis has not been made preoperatively, it is imperative to establish such a diagnosis before performing radical pneumonectomy. It is usually possible to remove a lymph node suspected of being the site of metastasis without contaminating the operative field with cancer cells.

When a histologic diagnosis has been established, the only findings in our experience which prevent radical pneumonectomy from being performed consist of either massive matted invasion of the mediastinal lymph nodes, direct invasion of the aorta on the left or extensive invasion of the superior vena cava on the right. It is infrequent to find invasion of the pulmonary veins of such extent as to contraindicate the performance of a pneumonectomy. A short pulmonary artery stump can always be closed with a continuous suture. Involvement of the pulmonary veins as far as the wall of the left atrium can be taken care of by applying a non-crushing clamp to the wall of the left atrium, removing all of the pulmonary veins and some of the atrial wall. The wound in the atrium is then repaired with a running suture. Similarly invasion of the main bronchus up to the trachea does not prevent the performance of peumonectomy. Even in the usual case it is our practice to divide the trachea obliquely just beyond the bronchus so as to leave no bronchial stump. (Fig. 3.)

The radical pneumonectomy is begun on either the right or left side by incising the mediastinal pleura from the apex of the chest down to the main bronchus. This incision is then extended anteriorly to expose the pulmonary artery and posteriorly to expose the bronchus and the carinal nodes. On the right side (Fig. 2) the azygos vein is doubly ligated and divided. Making traction on the divided stumps of the veins, the parietal pleura is elevated from the underlying structures from the main bronchus to the apex of the chest. This exposes the fat and lymph nodes overlying the upper esophagus, trachea and superior vena cava. Care is taken not to injure the phrenic nerve in this process. The vagus nerve is ligated and divided just below the point where the recurrent laryngeal nerve passes around the right subclavian artery. Making traction on the divided distal stump of the

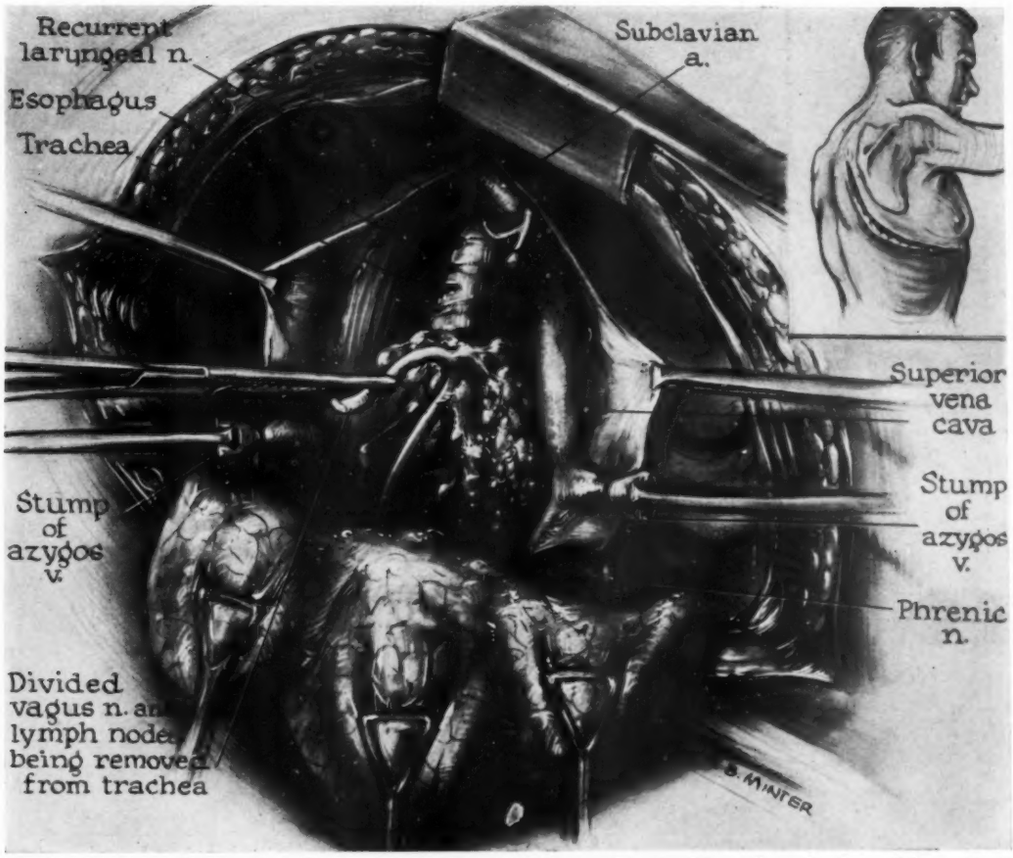

FIG. 2. Drawing illustrating the removal of the superior mediastinal lymph nodes in a right radical pneumonectomy.

vagus nerve, the mass of fat and lymph nodes overlying the anterior and lateral walls of the trachea are swept downward by sharp and blunt dissection. Included in this mass of fat and lymph nodes will be the occasional nodes which overlie the esophagus and those lying between the superior vena cava and the anterior flap of pleura. When this dissection is completed, the entire intrathoracic portion of the trachea, upper esophagus and superior vena cava will lie bare of all fat and lymph nodes. (Fig. 2.) During this dissection the upper lobe of the lung is drawn caudad by broad triangular clamps applied to the lung, taking care not to crush infected tissue or tumor.

The dissection is then carried anteriorly to expose the pulmonary artery and the superior pulmonary vein. Excellent exposure of the entire pulmonary artery up to its origin from the main pulmonary artery can easily be attained by retracting the superior vena cava anteriorly. The vena cava need not be occluded by this traction. Only in rare instances will it prove advisable to approach the most proximal portion of the right pulmonary artery by separating the parietal pleura from the superior and lateral surface of the vena cava and retracting the cava posteriorly. This is, however, a useful maneuver to remember if there is a bulky hilar tumor which makes access to the pulmonary artery difficult. We have not as yet found it necessary to divide the superior pulmonary vein before ligating and dividing the pulmonary artery on the right as has been suggested by Sweet.[13] Such a maneuver merely exposes the more distal portion of the pulmonary artery, whereas the long main stem of the pulmonary artery lying posterior to the superior vena cava is the portion of the vessel which must be widely exposed.

The pulmonary artery is then divided between ligatures. Any rather thick, nonabsorbable suture material may be used, such as heavy silk, cotton, or linen. Fine strong suture material may cut through the vessel wall when it is drawn up and tied. The distal

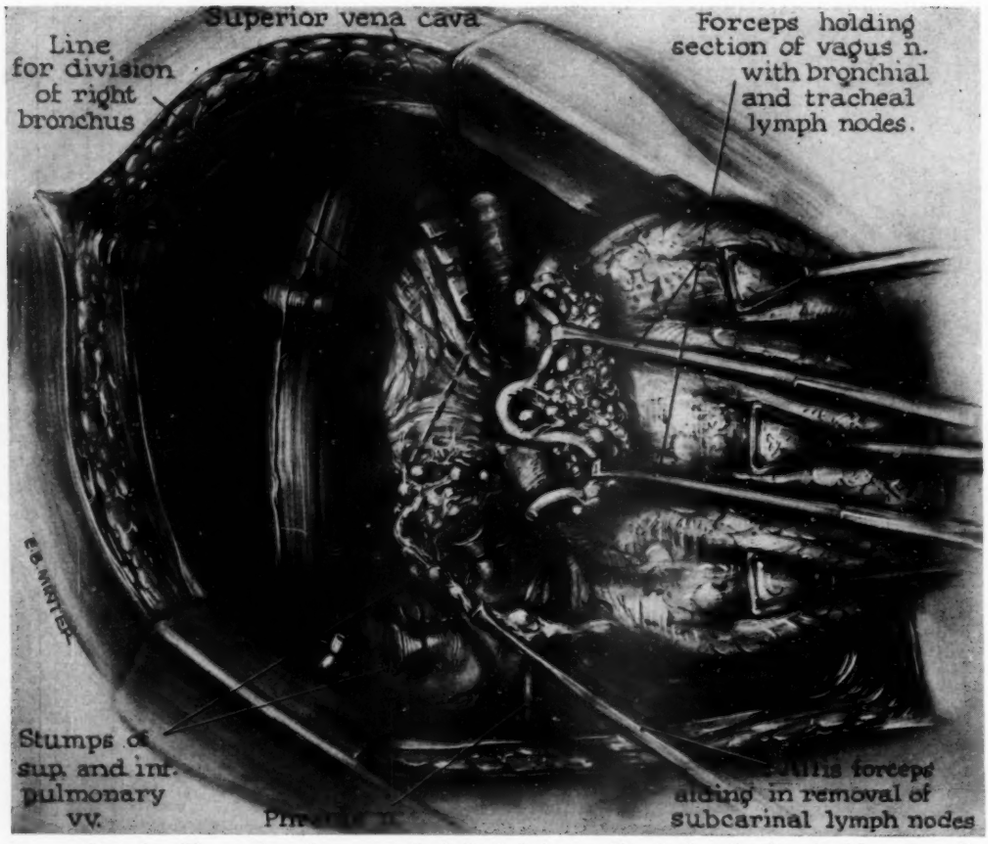
Superior vena cava
Line for division of right bronchus
Forceps holding section of vagus n. with bronchial and tracheal lymph nodes.
Stumps of sup. and int. pulmonary vv.
subcarinal lymph nodes

FIG. 3. Drawing illustrating the removal of the inferior mediastinal and subcarinal lymph nodes in a right radical pneumonectomy.

portion of the artery is ligated first. If the tumor is at a safe distance, we are apt to employ two distal ligatures—one around the branch to the upper lobe and the other around the branch to the lower and middle lobes. The proximal ligature is then passed around the vessel and tied close to the main pulmonary artery. It is our practice to place a second proximal ligature of the same material. This ligature is carried on a curved needle which transfixes the artery 2 or 3 mm. distal to the proximal ligature. This transfixing ligature is tied with a square knot on one side of the vessel. One of the free ends is then passed again around the vessel and the free ends tied a second time on the other side of the vessel. It is a common mistake for beginners using this technic to place the transfixing ligature at too great a distance from the proximal ligature which may have a tendency to slip off and in any event, the cuff of artery distal to the transfixing ligature will be shortened. There should always be a wide, flared stump of the artery distal to this ligature.

The superior pulmonary vein is isolated next. The ligatures are then applied as for the pulmonary artery. It is always advisable, if possible, to apply the distal ligatures to branches of the superior pulmonary vein in order to provide a longer stump distal to the proximal ligatures. If the cancer is in the hilar area, it is our invariable practice to open the pericardium in order to expose a greater length of the superior vein for safe ligation. A second transfixing proximal ligature is employed in the same manner as for the pulmonary artery. As mentioned previously, if the tumor is close to, or is invading, the superior vein, a light non-crushing clamp is applied to the auricular wall, the entire vein is removed and the wound in the atrium repaired with a running suture of No. oooo deknatel® silk.

The dissection is continued by reapplying the lung clamps so as to draw the lung anteriorly. The pulmonary ligament is divided up to the inferior pulmonary vein. All the lymph nodes overlying the esophagus are swept upward during this process and the main trunk of the

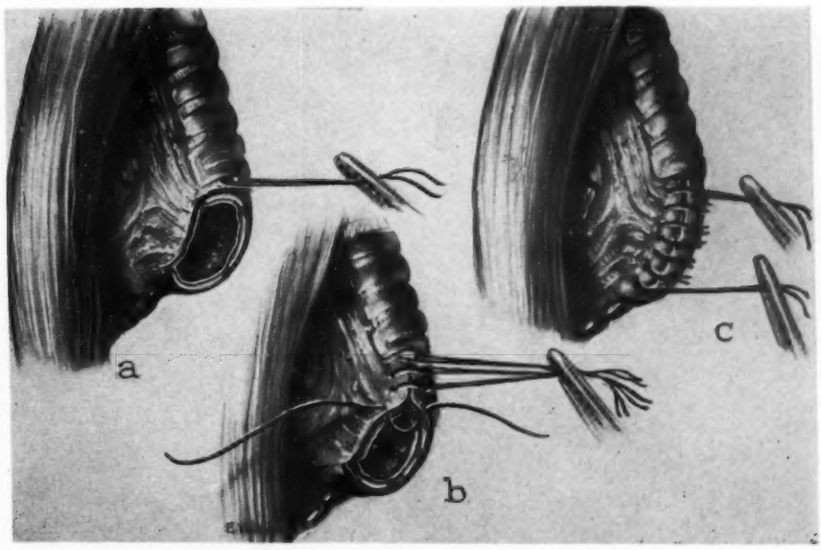

FIG. 4. Drawing illustrating the technic of closure of the tracheal wound after amputation of the right bronchus in a pneumonectomy. (*a*), Traction on a suture placed prior to amputation of the bronchus keeps the field exposed; (*b*) technic of placing interrupted sutures to close the trachea so that the mucous membrane is not traversed by the non-absorbable suture material; (*c*) the closure completed. The suture line is always reinforced by buttressing it against viable adjacent tissue.

vagus nerve is again divided low in the thorax. These lymph nodes and the isolated segment of the vagus nerve are held upward on the posterior surface of the lung by clamps. (Fig. 3.) The inferior pulmonary vein is then ligated and divided in the same manner as described for the superior pulmonary vein. Removal of the subcarinal lymph nodes is then begun. This dissection is started along the caudad margin of the opposite main bronchus at a distance of at least 3 cm. from the carina. These lymph nodes are then separated from the opposite main bronchus (Fig. 3) and are also drawn up to the lung leaving the carina and main bronchus bare.

The dissection has now been completed and the main bronchus is ready for division and closure. The lung with the attached lymph nodes and fat is retracted in the direction which will provide the best exposure of the bronchus and lower trachea. A clamp is placed across the main bronchus distal to the proposed line for division of the bronchus to prevent mucus or pus excaping into the operative field. No proximal clamp is used. A traction suture of No. 30 cotton on a fine french needle is passed through the lateral tracheal wall just above the line of the proposed incision. (Fig. 4*a*.) The lower trachea is then divided along an oblique line as indicated in Figure 3. It should be emphasized that in all cases the incision is made through the trachea and not the bronchus. This is done in order to avoid leaving any bronchial stump in which secretions can collect. In some instances when the tumor is not too bulky, the incision is not completed immediately, but is only carried through half its length. Traction on the lung as well as on the suture in the tracheal wall then aids in the exposure of the tracheal wound for careful closure. Generally, however, the incision is completed at once and the lung removed from the operative field as this affords better exposure for suture of the tracheal wound. As soon as the trachea is opened, the opposite main bronchus and the trachea are aspirated of any blood or secretions present.

The wound in the trachea is closed with interrupted stitches of No. 30 cotton on a fine french eye needle. Care is taken to see that the needle and the suture do not pass through the mucus membrane of the trachea. In most cases, it is surprisingly easy to do this. (Fig. 4*b*.) This suturing technic approximates mucosa to mucosa, yet leaves no suture material within the lumen of the trachea. This step in the technic we believe avoids ulceration, infection, granulation tissue and bleeding along the line of closure of the tracheal wound. The interrupted stitches are placed approximately 2 to

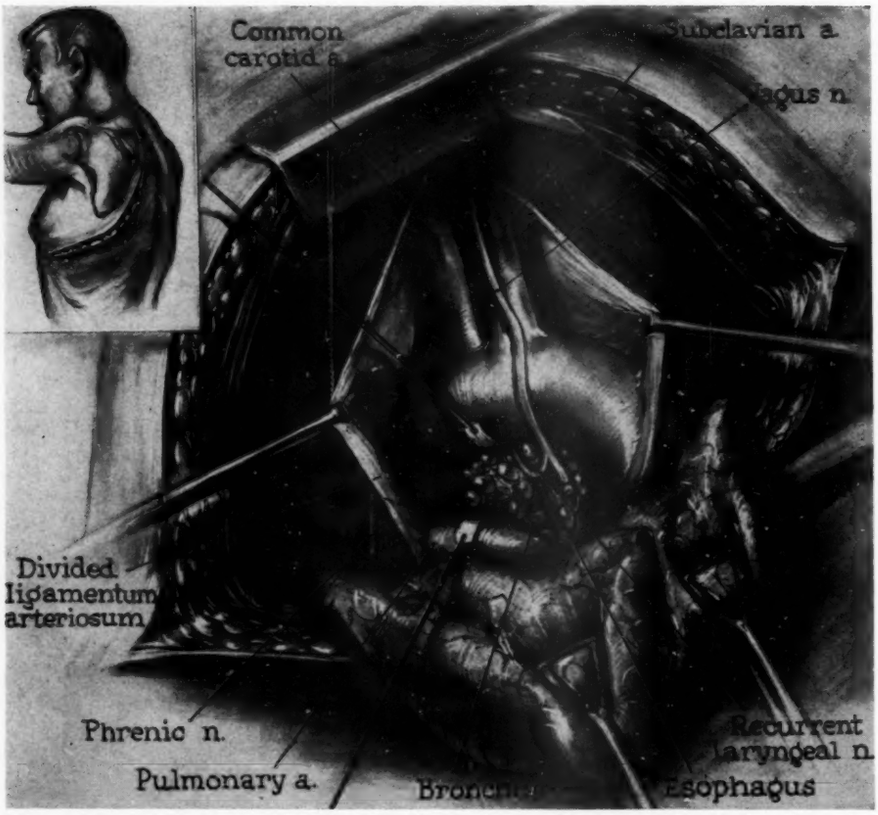

FIG. 5. Drawing illustrating the completed removal of mediastinal lymph nodes superior to the aortic arch, prior to the removal of the lymph nodes inferior to the arch, in a left radical pneumonectomy.

3 mm. apart. The suture line is reinforced with additional stitches if it is considered necessary. An attempt is always made to have the closed tracheal wound lie in immediate contact with some neighboring tissue. We formerly were in the habit of suturing a pedicled flap of parietal pleura over the suture line. More recently we have been using any available tissue in the immediate vicinity to buttress the suture line.

A left radical pneumonectomy is performed in a manner almost identical with the aforedescribed procedure on the right side. The presence of the aortic arch, however, crossing the field of the cephalad node dissection makes it impossible to perform the theoretically ideal block removal of fat and lymph nodes. (Fig. 5.) The mediastinal pleura is opened from the apex of the chest to the hilum of the lung. All fat and lymph nodes overlying the left common carotid and left subclavian arteries are swept downward over the aortic arch leaving these vessels and the vagus nerve cleanly exposed. Care must be exercised during this procedure to avoid injuring the left recurrent nerve as it passes upward between the trachea and the esophagus. The recurrent nerve is then identified as it passes around and beneath the aortic arch. It should be kept clearly in view during the subsequent lymph node dissection as it can be easily injured inadvertently. The vagus nerve is ligated and divided just beyond the left recurrent branch. The ligamentum arteriosum is then divided. Traction on the divided stumps of this ligament helps to provide exposure of the lymph nodes around the main bronchus and lower portion of the trachea. The aortic arch is elevated as much as possible from the trachea and the esophagus. Beginning high up beneath the aortic arch all the fat and lymph nodes lying anterior and lateral to the trachea and lateral to the esophagus are swept downward by blunt and sharp dissection to the distal portion of the left main bronchus. The dissection from here on differs in no essential way from that described previously for the right side, except that the pericardium is almost invariably opened on the left to expose the most proximal portion of the left pulmonary artery.

Before closing the wound in the chest, the

pleural cavity is washed with salt solution which is then aspirated. With the salt solution lying in the mediastinum, the anesthetist increases the intratracheal pressure to test the bronchial stump for leakage of air. If any leak is present, the stump must be exposed and the air leak closed. The pleural flaps overlying the upper mediastinum are loosely approximated, as this may aid in the more rapid sealing off of the mediastinum. Patients who have had a radical pneumonectomy, however, will always show some subcutaneous emphysema in the neck because coughing in the postoperative period will inevitably force air into the mediastinum and up into the neck. The ribs above and below the one resected are then drawn toward one another by any suitable rib approximator. The periosteum of the resected rib is closed with a continuous suture of No. 0 chromic catgut, which is interrupted once. In our experience a continuous suture gives a more airtight closure than interrupted sutures. The suture line is reinforced with a number of interrupted stitches of non-absorbable suture material spaced at a distance of from 2 to 3 cm. The serratus magnus, the latissimus dorsi and the trapezius muscle, if it has been divided, are closed with interrupted stitches. Drawing the arm down to the side and sliding the scapula posteriorly and caudad on the chest wall relieves tension on these muscles and facilitates closure. The deep layer of the superficial fascia is approximated with fine interrupted cotton with buried knots, taking care to align the skin accurately guided by the previously made scratch marks. The skin is closed with interrupted cotton sutures.

A small gauze dressing is applied to the wound. This in turn is covered with strips of wide elastoplast® adhesive. The skin is painted with compound tincture of benzoin which is allowed to dry before applying the elastoplast. The elastic adhesive should be only gently stretched when it is applied, since overstretching will blister the skin beneath it. The adhesive should extend well beyond the midline both anteriorly and posteriorly. This elastic adhesive dressing gives an excellent support to the wound during the act of coughing during the postoperative period. This original dressing may be removed and replaced with a light gauze dressing by the fourth or fifth day if desired. Skin sutures are removed on the seventh day. Before the patient leaves the operating room, intrapleural pressure on the operated side should be adjusted to normal values. This is best done after the patient has been returned to the supine position. A needle is inserted in the pleural cavity of the operated side anteriorly in the second interspace at a sufficient distance from the sternum to avoid injury to the internal mammary vessels. Sufficient air is then withdrawn to leave the intrapleural pressures, with quiet respiration, in the neighborhood of minus 2 to minus 10 cm. of water.

SUMMARY

A brief analysis of a series of 617 patients with cancer of the lung is presented. The results of surgical treatment are reported and the technic of radical pneumonectomy described.

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Lung Cancer Associated with Cancer Primary in Other Sites

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MULTIPLE cancers originating in different anatomic sites of the same individual have frequently been observed. Up to 1932 this phenomenon had been noted both in life and at autopsy in 1,259 instances.[10] For the most part they have grouped themselves in organs that are part of the same anatomic and physiologic system, but they are also found in sites that seem to have no particular interrelationship.

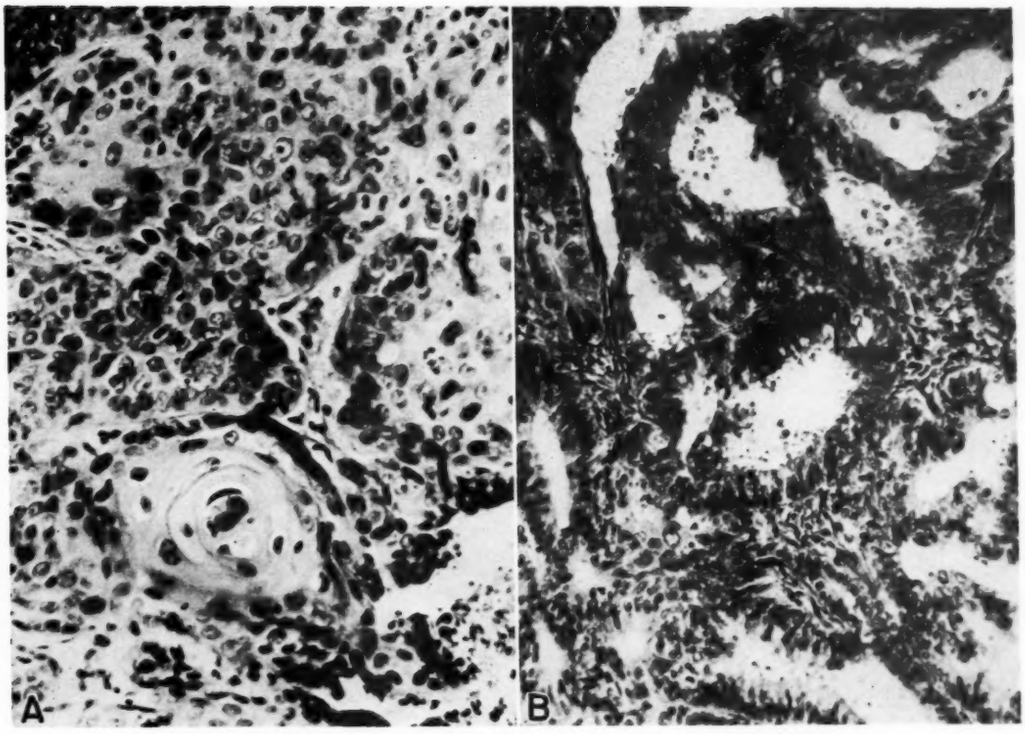
Warren and Gates[10] performed 2,829 autopsies on patients with cancer and found 194 instances of multiple primary malignant growths —an incidence of 6.8 per cent. On the basis of these data they concluded that an individual with one cancer is eleven times more apt to have a second develop than is a patient in whom the first cancer has not yet developed. The authors also stated that an average interval of 3.2 years elapsed between the appearance of the individual neoplasms, when this could be measured.

If this predisposition to develop multiple malignant tumors exists in certain individuals, it is reasonable to suppose that as survival rates are extended by a combination of earlier diagnosis and improved methods of treatment, new cancers can be expected to arise in new sites. Therefore, in follow-up examinations, patients who have had cancer should be scrutinized for evidence of a separate primary growth as well as for metastases from a lesion already known to exist.

The management of multiple primary cancers may seem at first to be exceedingly complex. Indeed, in those occurring synchronously it is often difficult to decide what form of therapy to employ and which tumor deserves first consideration therapeutically, or if both should be treated at once. In metachronous lesions there is less confusion, for the time interval between the appearance of the separate tumors usually permits an estimation of the degree of control of the first lesion and a more deliberate selection of the treatment for the second.

It has been assumed that the possibility of survival diminishes with the advent of each new cancer capable of metastasizing. Yet, it is more and more suggestive as experience accumulates that the maintenance of aggression in treatment, rather than the yielding to defeatism, has produced surprisingly favorable results. In the series to be reported herein eight of eighty-two patients survived five or more years after treatment of their multiple cancers, one of which occurred in the lung. Consequently, we believe that the appearance of two or more primary cancers of different organ systems should not contraindicate radical therapy for each. If, for example, adenocarcinoma of the rectum has been controlled by abdominoperineal resection and later carcinoma of the breast develops, it should be treated by radical mastectomy. Similarly, the apparently complete eradication of a malignant testicular tumor several years prior to the appearance of gastric cancer would not contraindicate gastrectomy.

The probability of survival in each separate case of cancer varies considerably with the particular clinical setting. If the carcinoma of the rectum just mentioned occurred by itself and were in the pathologic classification of Duke's A or Duke's B, the patient would have an estimated 65 to 85 per cent chance of living five years. If the breast cancer that was removed subsequently were the only tumor present and was found not to have metastases in the regional lymph nodes, the chance of five-year survival would be approximately 75 per cent. One can only conjecture whether the combination of these two primary lesions in one individual would alter the prognosis. Actually, the prognosis may be even better than that reported for such notorious cancers as those of the stomach or esophagus occurring alone.



1A 1B

FIG. 1. Case 11. A, squamous carcinoma of the hard palate. B, adenocarcinoma of the lung in the same patient.

In facing repeated major surgical procedures patients and their families need psychologic help, but respond well when a reasonable chance of "cure" is offered. Thus, a forty-nine year old mother of four children did not protest when she was faced with the necessity of radical mastectomy, anterior resection of the sigmoid colon, and right upper and middle lobe lobectomy—the last two operations within two months of each other.

CRITERIA FOR MULTIPLICITY

Criteria for diagnosis of multiple cancers must be clearly defined. In the first two examples cited previously (carcinoma of the rectum followed by breast cancer and a malignant testicular tumor followed by gastric cancer) the combinations of lesions were such that the second primary, because of its location, was not likely to be confused with metastases from the first. However, when lung tumors are considered, a careful distinction must be made as to whether this organ is acting as the site of a new growth or as a filter and repository of metastases. This distinction can be made unequivocally only when the two tumors have entirely different histologic characteristics, as in Case 11 (Table III) in which squamous carcinoma of the hard palate coexisted with adenocarcinoma of the lung. (Fig. 1.) There are twenty-six cases in this series meeting this criterion (excluding seventeen cases with basal cell carcinomas of the skin). The former are classified as having *positive* evidence of multiple primary cancers.

On the other hand, if the two lesions in question have the same histologic pattern, it is almost impossible to distinguish microscopically between a new, primary focus and metastasis in the lung. By no means, however, does this necessarily exclude the possibility that the pulmonary lesion may be a separate and distinct primary one. Reliance in these instances must be placed upon the clinicopathologic picture, and in this series thirty-eight cases are classified as having *probable* evidence of multiple primary cancers. In Case 19 (Figs. 8 and 9) squamous carcinoma existed synchronously in the extrinsic larynx and the left main stem bronchus. The latter is an unusual site for metastasis from the former, and in the gross specimen removed by radical pneumonectomy, cancer was found arising from the bronchial

wall. There were no metastases noted in the remainder of the resected lung, nor have any appeared subsequently in the regional lymph nodes of the neck or in the opposite lung in the five years and five months since operation. In Case 32 squamous carcinoma, confined to the edge of one vocal cord and non-infiltrative in character, occurred synchronously with epidermoid carcinoma of the right upper lobe bronchus. The pathologist believed that the probability that the two lesions represented primary cancer and its metastasis was remote, despite the presence of the same basic histologic pattern.

TABLE I

MULTIPLE PRIMARIES ASSOCIATED WITH LUNG CANCER*

Total cases of lung carcinoma	2,502
Total multiple primaries	81
Incidence	3.2%

* From the files of Memorial Center.

In addition to these gross observations, the pathologist will sometimes find in the bronchus *in situ* carcinoma confluent with bronchogenic carcinoma suggesting the bronchial origin of the cancer.

In a separate group are seventeen cases of lung cancer associated with basal cell carcinomas of the skin. Although these skin lesions are non-metastasizing, their presence in combination with another malignant growth stresses the possible inherent tendency of some individuals to evolve cancer.

COMPILATION OF CASES

In 2,502 cases of cancer of the lung observed in Memorial Center over a period of twenty-eight years (up to 1954), there have been eighty-one instances in which the lung tumor was one of two or more separate primary malignant growths—an incidence of 3.2 per cent. (Table I.) There were two triple primaries.

Warren and Gates[10] found 120 cases of lung cancer in their autopsy series, in nine of which there was another primary lesion—an incidence of 7.5 per cent. They constituted 4.6 per cent of all the cases found to have multiple primary cancers at autopsy.

The sites of the separate malignant growths in our series are listed in Table II and include eighteen of the oral cavity, nineteen of the larynx (both extrinsic and intrinsic), five of the colon and rectum, and three each of the bladder, kidney and squamous carcinoma of the skin, one of the breast and two each of the testicle, Hodgkin's disease and lymphatic leukemia. There was one each of the prostate, breast, cervix, common bile duct, branchiogenic cyst cancer, and one soft part sarcoma. The triple primary cases included one patient who had cancer of the breast and sigmoid, and another who had cancer of the tongue and extrinsic larynx.

TABLE II

MULTIPLE PRIMARIES ASSOCIATED WITH LUNG CANCER

Double Primary	
Head and Neck	
Lip	2
Alveolar ridge	2
Buccal mucosa	1
Tongue	6
Floor of mouth	3
Hard palate	2
Tonsil	1
Extrinsic larynx	11
Intrinsic larynx	8
Branchiogenic cyst	1
Breast	1
Colon	
Sigmoid	3
Rectum	2
Genitourinary	
Testicle	2
Prostate	1
Bladder	3
Kidney	3
Lymphoma	
Hodgkin's disease	2
Lymphatic leukemia	2
Cervix	1
Common bile duct	1
Soft part sarcoma	1
Skin	3
Basal cell carcinoma of skin	17
Triple Primary	
Breast and sigmoid	1
Tongue and extrinsic larynx	1
Total cases	81

In the literature [8–11] there are at least thirty-seven cases in which cancer of the lung has been found to be one of two malignant tumors at autopsy. Of these the kidney, colon and stomach were the sites of the other tumor five times; the skin, four times; the prostate and breast, three times each; the esophagus, gallbladder and tongue, twice each; and the lip, bladder, larynx, liver, sarcoma of the leg and lymphosarcoma, once each. In addition, there was a triple primary arising synchronously as squamous carcinoma of the bronchus, adenocarcinoma of the pancreas and carcinoma of the prostate.

Synchronous and Metachronous Cancers. In a discussion of multiple primary malignant

growths the time relationships between the appearances of the tumors is of interest. In this communication the cancers are considered synchronous if the interval between the establishment of the diagnosis of the first primary tumor and the detection of the second was less than six months; metachronous, if more than six months.

In the sixty-four cases in this series, excluding the cases associated with basal cell carcinomas, lung cancer was synchronous with another malignant tumor in twenty-four instances, and in forty instances it was metachronous.

In four of the forty metachronous cancers, lung cancer antedated the appearance of the second primary malignant tumor; two of these were in the extrinsic larynx, one was in the descending colon and Hodgkin's disease developed in one patient. The interval in these four cases ranged from six months to four and a half years. This finding may be considered as additional evidence that prolonged survival after the removal of one cancer may well permit the formation of a second at another site. In this connection, in the original paper from this institution[2] which listed twenty-five multiple primary cancers of the type under discussion, not one case was reported in which a lung lesion antedated the appearance of the second growth. This is also true for the majority of the cases reported in the literature.

DIAGNOSIS

When a patient who has cancer known to metastasize develops pulmonary symptoms or an asymptomatic roentgenographic shadow whose significance is not clear, considerable clinical and laboratory data may be required to establish the true nature of the process.[5]

History and Physical Examination. Although primary cancer of the lung may be expected to show earlier evidences of bronchial irritation and stenosis than metastasis, little reliance can be placed on signs and symptoms as aids in differentiating between the two.

Sex and Age. There were seventy-two men and nine women in this series. Their ages varied from thirty-five to eighty-four years, with an average of 59.3 years.

Roentgenographic Findings. The fact that seventeen cases were asymptomatic and were detected by routine roentgenograms of the chest emphasizes the value of these films as part of a follow-up system. Once the diagnosis of cancer capable of metastasizing is made, it has been customary to order x-rays of the lungs at intervals varying with the virulence of the known malignant tumor, but not less frequently than every six months.

It is impossible to establish with certainty the nature of a solitary shadow of the lung by roentgenographic means alone. Nevertheless, the correct diagnosis of primary lung cancer, as distinguished from metastasis, was suggested in sixty-eight instances, largely by the fact that certain cancers are known to metastasize infrequently to the lung. In addition, the pulmonary shadow's configuration with its associated segmental atelectasis and the inability to demonstrate other suggestive opacities radiologically gave further emphasis to this possibility. It is fundamentally important that the radiologist be aware that such a differential diagnosis exists, and bring this possibility to the attention of the clinician.

Additional aid in evaluating pulmonary shadows in this category may be derived from comparison with previous chest roentgenograms, and every effort should be made to obtain them. At Memorial Hospital it is believed that an orderly progression of radiologic technics should be maintained. Whereas these technics may increase the possibility of revealing lesions not shown by ordinary roentgenograms, they should be used for a specific purpose and not ordered routinely. For the most part, in addition to the ordinary sagittal and lateral views of the chest, stereoscopic postero-anterior views are taken. Occasionally these stereoscopic views are taken in the lateral projection. If doubt persists, the relatively expensive procedure of tomography can be used to define doubtful shadows seen on the previous films, and to help reveal bronchial changes in the absence of atelectasis.

It is tempting to assume that a single shadow in the lung in the presence of cancer is metastasis, and that it may represent the forerunner of many to come. However, undue delay in aggressive therapeutic action while attempting to gain a panoramic view by a series of x-rays over a period of time increases the probability that primary cancer or a solitary metastatic deposit may elaborate itself and become incurable.

Bronchoscopy and Exfoliative Cytology. Papanicolaou[6] states that in sputum or bronchial

aspiration containing clusters of cells the pathologic varieties of primary lung cancer can often be distinguished. In twelve cases it was possible to make a definite preoperative diagnosis of pulmonary cancer by obtaining histologic material which proved different from that of the

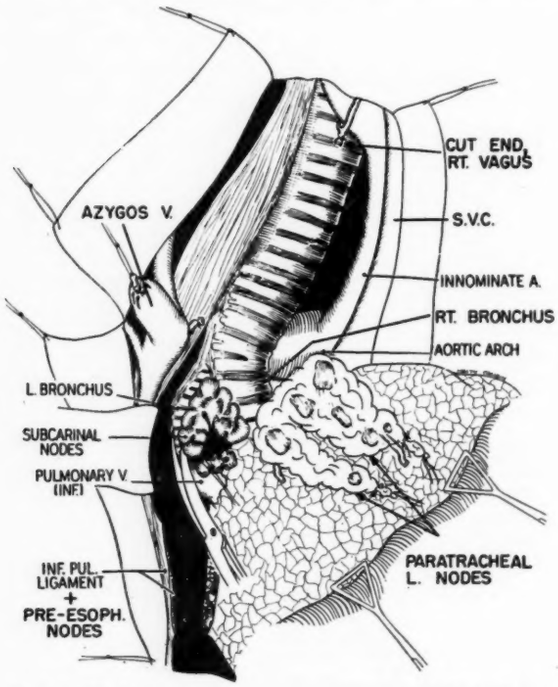


FIG. 2. Right radical pneumonectomy. A block dissection of the paratracheal, subcarinal and pre-esophageal lymph nodes with the lung is shown. The right bronchus is not divided. Note recurrent laryngeal nerve with divided stump of right vagus which has been excised. Azygos vein is retracted. (S.V.C. = superior vena cava.) See Figure 3.

other primary cancer. For example, in Case 45 a correct diagnosis was made when the first cancer was adenocarcinoma of the rectum and the cytologic picture of the bronchial washings was squamous carcinoma. Radical pneumonectomy was performed which confirmed the nature of the lung lesion.

In these eighty-one cases there were thirty-four instances in which the cytology of the bronchial secretions was positive. In six of these cases exfoliative cytology alone was able to make a diagnosis of cancer of the lung. In two other cases the cytology as well as the biopsy was positive, and in four cases the cytology failed to yield a positive diagnosis. Bronchoscopic biopsy helped clarify the differential diagnosis in two cases by distinguishing squamous carcinoma of the bronchus from Hodgkin's disease, and oat-cell carcinoma from squamous carcinoma of the extrinsic larynx. Two cases were established preoperatively by aspiration biopsy through the chest wall.

When the cells obtained by exfoliative cytology reveal the same histologic structure as the known primary cancer elsewhere, it is impossible to distinguish whether metastasis is present. However, the fact that carcinoma is revealed by this method is often a help in establishing the true nature of equivocal shadows. This was demonstrated in five of eighteen cases in which solitary metastatic foci rather than primary carcinoma of the lung were found. However, for the most part, metastases in the lung tend to yield scantier exfoliations than a primary malignant tumor.

Biopsy at Operation. In a number of instances it was impossible to make a preoperative histologic diagnosis by any clinical means; therefore exploratory thoracotomy was advised. This procedure is a relatively simple one, has a mortality of less than 1 per cent and very little morbidity. However, before surgery is undertaken every effort is made to evaluate the patient's cardiac and pulmonary function so that at operation it can be judged how much functional respiratory epithelium can be removed, if it is necessary.

Tumors located near the hilum and seeming to arise in, or immediately adjacent to, the main stem bronchus (as in Case 21) can be handled in two ways: (1) an aspiration biopsy of the main tumor mass can be made with the chest open; and (2) a wedge of tissue can be removed from a representative area. However, when the clinical setting strongly suggests that a primary tumor of the lung exists, it has been customary to perform radical pneumonectomy without an adequate biopsy.[3] (Fig. 2.) This provides the only means of securing a complete specimen for histologic study without incising the lesion itself, thereby reducing the risk of intrapleural dissemination of infection and/or neoplastic tissue. The inclusion of the mediastinal lymph nodes as part of a block dissection with the lung takes little more time, does not increase morbidity and improves the probabilities of removing all the gross evidences of cancer.

The problem of the management of solitary peripheral lesions at exploratory thoracotomy is more difficult, for if this were a primary carcinoma and the patient's reserve were adequate, radical pneumonectomy affords the best chance

for wide removal of cancer. If it is a solitary metastasis, one might tend to be more conservative in the amount of respiratory epithelium to be removed and thus perform radical lobectomy. (Fig. 3.)

In an attempt to distinguish the histologic nature of these peripheral tumors, wedge or segmental resection and even aspiration biopsy of these lesions has been used. These methods provide a quick pathologic diagnosis and have added significance if slides of the primary lesion elsewhere in the body are available for comparison. However, if the patient's condition permits, the aforementioned measures are usually omitted when it seems most probable that cancer is present and a radical lobectomy is performed.

Reasoning in a similar vein, as for the tumors of the hilum for which radical pneumonectomy was performed, it is believed that these peripheral lesions should be excised *in toto* with the affected lymphatics. This provides a wider and more complete excision of the tumor, and a better opportunity to distinguish the character of the lung growth by preserving its relationship to the bronchial tree. The inclusion of the lymph nodes implicit in radical lobectomy, although not as thorough a dissection as that of radical pneumonectomy, increases the probability of removing metastatic foci. The reason for this is that not only primary cancers of the lung but also metastatic deposits therein can give rise to daughter or second generation metastases in the local lymph nodes. On occasion, after radical lobectomy has been completed, if there is doubt whether or not there has been adequate excision achieved by this compromise procedure, and if the condition of the patient permits, a modified radical pneumonectomy can be completed.

On several occasions a roentgenographic finding of a single shadow was inaccurate in that multiple parenchymal nodules were found at exploratory thoracotomy. One of these is usually selected for frozen section; and if this is positive for the presence of cancer, nothing further need be done.

HISTOLOGIC TYPES

The histologic type of pulmonary neoplasm in this series was epidermoid carcinoma in sixty-three instances. Five patients had adenocarcinoma of the lung, four had anaplastic carcinoma, two had oat-cell carcinoma, two had

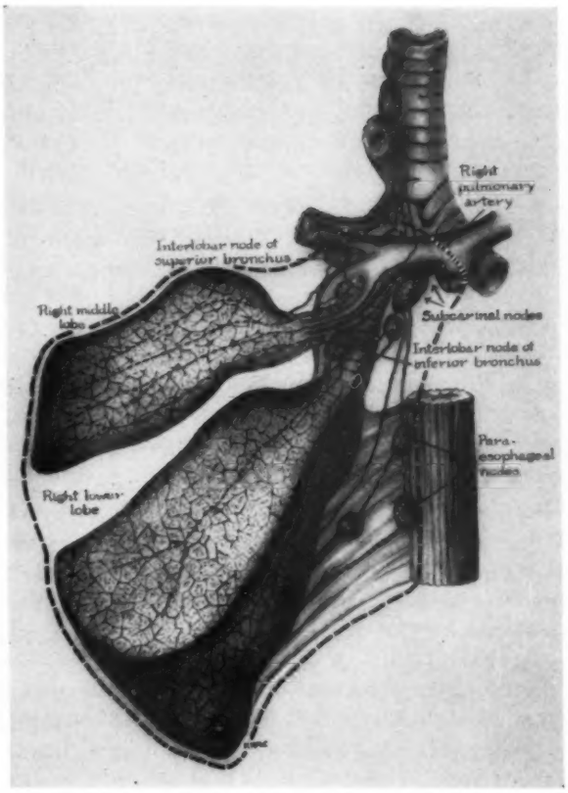


FIG. 3. Right radical middle and lower lobe lobectomy is indicated by the dotted line. Note how the nodes of the right paratracheal region are not included. (See Figure 2.) Stump of right upper lobe shown; lobe omitted for clarity.

mucous gland carcinoma, and two had spindle cell carcinomas. One patient had terminal bronchiolar carcinoma; one had extramedullary plasmacytoma and one had malignant bronchial adenoma.

TREATMENT

Of the eighty-one cases in this series, forty-two were surgically explored; twenty-three had simple or radical pneumonectomy and nine had either simple or radical lobectomy. This is a resectability rate of about 75 per cent, which is much higher than the average for operable primary lung cancer alone. Undoubtedly this reflects the relatively early stage in which most of these lesions were discovered.

There was one postoperative death after radical pneumonectomy and one after exploratory thoracotomy.

In the thirty-nine patients who were nonresectable, gold-filtered radon seeds were inserted in and about the cancer at the time of exploratory thoracotomy, and this was usually

supplemented by super voltage x-ray therapy in the postoperative period.

There were seven individuals who had no treatment directed to their primary lung cancer, either because it was too far advanced, they were too sick or had refused specific therapy. Most of these patients were dead within a three to four-month period after the diagnosis was made.

RESULTS

In this series of eighty-one patients there were eight who survived five or more years after their lung operation. Of these eight, a primary cancer, other than in the lung, had its origin in one case each in the hard palate, the extrinsic larynx and in the rectum. One five-year survivor had three primary cancers of the breast, colon and lung. The remaining four patients had basal cell carcinomas.

In this group seven had epidermoid carcinoma of the lung and one had extramedullary plasmacytoma. It is interesting to note that one of these survivors had both pulmonary vein invasion and parietal pleural involvement by cancer, and had had a simple upper lobe lobectomy. He died of a heart attack five years later, and no evidence of cancer was found at autopsy. There were two other patients (Cases 38 and 45) in whom the pulmonary vein was found on the excised specimen to be invaded by the lung cancer. Both of these patients have survived two years without evidence of disease so far, after radical pneumonectomy in each case.

Thirteen patients lived from one to four years after the pulmonary surgery, six of whom are without evidence of disease at the present time.

There were nine autopsies in this series, each one of which confirmed the presence of separate primary cancers. In two of these there was a chance finding of a second primary cancer occurring in the bladder and in the gallbladder.

The interval between the development of the first and the second primary growth ranged from 0 to 18 years, and there were fifteen instances in which this interval was five or more years.

Oral Cavity Cancers. One of the most interesting findings in this series is the occurrence of cancer in the head and neck region of thirty-six patients, which is by far the largest single anatomic group. Eighteen of these occurred within the oral cavity (Table III), and nineteen in both the extrinsic and intrinsic larynx (eleven extrinsic, eight intrinsic). One can only conjecture that this relatively high proportion of cancer in an anatomic system related to the lungs suggests a possible common etiologic agent or group of agents.

Several facts have become apparent and are worth emphasizing. Whenever cancers of the oral cavity or larynx occurred synchronously with lung cancer, the pulmonary lesion was the first to be treated when the patient's condition permitted it. This follows the principle that the more lethal disease deserves first consideration.

When one of the primary cancers involved the larynx, before the exploratory thoracotomy was performed, elective tracheostomy was performed and anesthesia administered through it. This obviated the necessity of introducing an endotracheal tube through a carcinomatous and infected area in the larynx (Fig. 9), and carrying it lower in the tracheobronchial tree. In addition, if an endotracheal tube were used without a tracheostomy, the threat of occlusion of the airway by laryngeal edema in the postoperative phase is a real one. Also, the maintenance of good toilet of the tracheobronchial tree under these circumstances is facilitated by the use of a tracheostomy.

When a patient has had a total laryngectomy, and in the course of time a cough develops, with or without the production of sputum, it is usually interpreted as tracheobronchitis. In at least three instances in this series this misinterpretation was made, and it was only with increasing cough and eventually hemoptysis that a roentgenogram of the lungs was advised and the pulmonary shadow that proved to be lung cancer was observed. Therefore, at this institution it has become a routine for all patients who have had cancer of the oral cavity or larynx, even though asymptomatic, to have a roentgenogram of their lungs every six months. Should they develop respiratory symptoms at any time before this interval, posteroanterior and lateral x-ray chest films are taken, and expectorated matter plus bronchial washings are studied for exfoliative cytology.

This principle of routine x-ray of the lungs as previously outlined should not be confined to those patients with oral or laryngeal cancer, but should be applied to cancer arising in other anatomic sites as well. The interval of six months is an arbitrary one and might be re-

duced in patients whose original cancer appears to be highly aggressive.

Solitary Metastases. Of the eighteen cases mentioned in which a solitary metastasis rather than primary carcinoma of the lung was found, the sites of origin included four cases with adenocarcinoma of the rectum, two with osteogenic sarcoma of the femur, one teratocarcinoma of the ovary, one leiomyoma of the uterus, one liposarcoma of the buttock, one malignant melanoma each of the gingiva, the skin of the back and the left ear lobe, one fibrosarcoma of the mandible, one papillary cystadenocarcinoma of the kidney, two rhabdomyosarcomas of the extremities, one mixed tumor of the left parotid, and one breast carcinoma.

In this group there are five alive and well five years after resection; there are five dead of disease, and eight who are living without evidence of disease ranging from one month to four years.

There are at least 150 reported cases of metastases surgically excised from the lung in the literature, and many of these have surprisingly long survival rates with no other metastases becoming evident.

DISCUSSION

There are several points that can be made from the aforementioned data:

1. Multiple primary cancers in unrelated systems can and probably will occur with increasing frequency as survival rates improve. Therefore, in all patients who have had a known malignant tumor constant vigilance should be maintained, not only for evidence of the spread of metastases but also for the initiation of a new primary cancer.

2. In a patient with cancer primary at another site capable of metastasizing, the appearance of a shadow in a roentgenogram of a lung, with or without pulmonary symptoms, may indicate the presence of a new primary cancer of the lung. In fact, in a similar period of time at this institution there were only eighteen solitary metastases occurring in the lungs, whereas there were sixty-four separate primary cancers of the lung. This would indicate that there is approximately a 3½ to 1 chance that a solitary pulmonary shadow is a separate primary lung cancer rather than a single metastatic deposit.

3. The appearance in a roentgenogram of a solitary pulmonary shadow synchronous with cancer from another site known to metastasize, should not depress aggressive action in the treatment of either lesion, if each tumor is potentially controllable by established therapeutic measures. In these synchronous tumors the more malignant or lethal should be treated first, if possible. In most instances this will be the lesion in the lung.

4. If the shadow in the lung appears metachronously with cancer at another site known to metastasize, some radiologic procedures, bronchoscopic biopsy or exfoliative cytology might aid in establishing not only the presence of cancer but also the possibility of a new primary lesion in the lung. Should all these measures remain equivocal, exploratory thoracotomy should be performed for diagnostic purposes.

5. If a pulmonary lesion arises in, or is immediately adjacent to, a main stem bronchus, radical pneumonectomy is the treatment to be preferred. If the lesion is more peripherally placed, radical lobectomy can be performed. The excision of the lymph nodes in a block dissection with the lung or lobe containing either a new primary or a metastatic focus, requires little additional surgical skill or time, adds no morbidity or mortality and improves the probability of removing all the cancer. Theoretically, at present, this affords a better opportunity for cure.

6. At exploratory thoracotomy when the lesion is found to be non-resectable, gold-filtered radon seeds may be inserted within the tumor and about its periphery, and supplemented by external radiation therapy in the postoperative period. This method of treatment has produced a measure of palliation and perhaps even prolongation of life in a sufficient number of patients to encourage its further use.

7. The preponderantly large association in this series between carcinomas arising in the head and neck and separate primary cancers of the lung should stimulate alertness for this possibility. The same vigilance about pulmonary shadows should be maintained for cancer in other sites.

8. The resectability rate of 75 per cent in this series of patients and the survival of eight for five years or more should encourage aggressive action in the treatment of multiple primary cancers.

TABLE III

Case No.	Patient, Age (Yr.) and Sex	Site of First Primary Tumor	Method of Treatment	Date Treated	Pathology	Time Interval	Site of Secondary Primary Tumor	First Symptom	Preoperative Diagnosis			Method of Treatment	Date Treated	Pathology	Follow-up
									X-ray	Cytology	Biopsy				
1	L. H., 52, M	Left lung	X-ray	7/41	Squamous ca., grade II	0	Lower lip	Ulcer	Observation		..	Refused surgery	.....	Squamous ca.	11/41, died of disease, 4 mo.
2	P. N., 49, M	Lower lip with bilateral neck metastases	Excision of lip; bilateral neck dissection	3/53	Squamous ca., grade II, with metastasis to right neck	1 yr.	Right lung	X-ray	x	0	..	Right upper lobe and right middle lobe lobectomy with chest wall resection	4/54	Epidermoid ca., grade III	9/20/54, no evidence of disease, 5 mo.
3	J. R., 65, M	Upper alveolus	X-ray	10/39 and 6/40	Squamous ca., grade II	10 mo.	Right lung	Cough, pain	x	..	x	X-ray	7/40	Squamous ca., grade II	No autopsy, 3 mo.
4	A. R., 65, M	Gingiva	X-ray	9/44	Squamous ca., grade II	0	Lung	X-ray	x	..	x	X-ray	10/44	Squamous ca., grade II, of trachea	5/45, died of disease, 7 mo.
5	J. K., 61, M	Floor of mouth; neck node metastasis	X-ray and radon	8/48–10/48	Squamous ca., grade II; metastasis level I	2¾ mo.	Left lung	Hemoptysis	x	..	x	Pneumonectomy	7/50	Squamous ca., grade III; negative nodes	11/50? cardiovascular accident or metastasis 4 mo. postoperatively
6	T. B., 47, M	Floor of mouth	Partial glossectomy. Right radical neck dissection and mandible	1949	Squamous ca., grade II	4½ mo.	Left lung	Pain and hemoptysis	x	..	x	Left upper lobe lobectomy and radon	8/54	Epidermoid ca.	9/54, no evidence of disease
7	A. O., 70, M	Floor of mouth	X-ray	10/42	Squamous ca., grade II	0	Lung	X-ray	..	..	x	X-ray	11/42	Epidermoid ca.	12/42, died of disease
8	A. P., 64, M	Tongue	X-ray, radical neck dissection	1/32–6/32	Squamous ca., grade II	14 mo.	Right lung	X-ray	x	..	..	None	8/33	Squamous ca.	9/33, died of disease
9	R. P., 65, M	Tongue	Glossectomy	9/47	Squamous ca., grade I	0	Lung	X-ray	x	x	x	X-ray	9/47	Epidermoid ca.	4/48, died of disease
10	J. L., 49, M	Tongue	Total glossectomy, left comedo	5/50	Squamous ca., grade II, metastasis to 1 node	2 mo.	Right lung	Pain	x	x	..	Right upper lobe lobectomy	5/52	Squamous ca., grade II, right upper lobe to upper pulmonary vein invasion	9/52, died of disease; *in situ* ca. in adjacent bronchus

11	L. H., 69, M	Tongue	Glossectomy, laryngectomy (x-rays 5 yr. previously), radical neck dissection	4/52	Adenocystic ca.	0	Left lung	Abscess on x-ray	x	x	..	Too late for treatment; disease established by cytology	10/53	Epidermoid ca.	7/54, died of disease
12	L. V., 71, M	Tongue, neck nodes	Hemimandibulectomy, hemiglossectomy	8/54	Squamous ca., grade II; neck node metastasis	0	Right lung	X-ray	x	..	..	Radical right lower lobe lobectomy	7/54	Adenocarcinoma with metastasis to peribronchial lymph nodes	8/24/54, no evidence of disease
13	M. M., 50, F	Tongue	4/49 excision and x-ray 12/51 partial glossectomy and excision of floor of mouth for recurrence	.....	Squamous ca., grade II	42 mo.	Right lung	Cough	x	..	..	Right lower lobe and right middle lobe lobectomy	6/54	Bronchogenic squamous ca., grade III	9/54, living and well; ? disease
14	D. N., 69, M	Hard palate	Radical treatment	1947	Squamous ca.	2 mo.	Right lung	Chill, malaise	x	..	..	Radical pneumonectomy	4/49	Extramedullary plasmacytoma	4/54, no evidence of disease, 5 yr.
15	W. B., 55, M	Palate	X-ray	8/49	Squamous ca., grade II	0	Lung	X-ray	x	..	x	Left pneumonectomy	9/49	Bronchogenic adenocarcinoma, negative nodes	2/50, died of disease, 5 mo.
16	M. McT., 52, F.	Buccal mucosa	X-ray, excision	1948	Squamous ca.	1 mo.	Left lung	Cough	x	x	..	Pneumonectomy	9/49	Squamous ca., grade II; intrapulmonic node	4/50, died of disease
17	S. K., 59, M	Left lung	Simple pneumonectomy	3/41	Epidermoid ca. of bronchus	2 mo.	Tonsil	Hoarseness	..	..	x	Radon	5/41	Epidermoid ca.	Widespread metastases, 4 mo.
18	A. H., 62, M	Ext. larynx; pyriform sinus	X-ray, radical neck dissection	1941	Squamous ca., grade III	4 mo.	Left lung	Cough, pain	x	..	..	X-ray	12/45	Mucous gland ca.	1/46, died of disease
19	L. B., 64, M	Ext. larynx	Laryngectomy	5/49	Squamous ca., grade II	0	Lung	X-ray	x	x	..	Pneumonectomy	3/49	Squamous ca., grade II; nodes clear	8/54, no evidence of disease, 5 yr., 5 mo.
20	H. S., 54, M	Left lung	Radical pneumonectomy	10/50	Adenocarcinoma, grade III, with mediastinal node dissection	26 mo.	Ext. larynx	Dysphagia	x	x	..	Laryngectomy	1/53	Epidermoid ca., grade III, with bilateral neck metastases	6/29/54, no evidence of disease 1½ yr.

TABLE III (*Continued*)

Case No.	Patient, Age (Yr.) and Sex	Site of First Primary Tumor	Method of Treatment	Date Treated	Pathology	Time Interval	Site of Secondary Primary Tumor	First Symptom	Preoperative Diagnosis			Method of Treatment	Date Treated	Pathology	Follow-up
									X-ray	Cytology	Biopsy				
21	T. H., 49, M	Ext. larynx	X-ray	10/51	Squamous ca., grade II	0	Right lung	X-ray	..	x	x	Right radical pneumonectomy	10/51	Epidermoid ca. invading pulmonary vein	11/52, died of disease, 13 mo.
22	C. D., 48, M	Ext. larynx	X-ray	12/39	Squamous ca., grade II	13 yr.	Right lung	Pain, "pneumonitis"	x	Failed	x	None	10/52	Oat cell ca.	10/52, died of disease and pneumonia
23	J. H. F., 55, M	Ext. larynx	Total laryngectomy	10/44	Epidermoid ca., grade III	8 yr.	Right lung	Cough	x	..	x	None—too sick	5/52	Bronchogenic ca.	7/62, died of disease, no autopsy
24	S. F., 64, M	Ext. larynx with metastasis	X-ray	8/53	Squamous ca., grade II	0	Left lung	Cough	x	..	x	Exploratory thoracotomy	8/53	Anaplastic ca.	Lost to follow-up
25	M. S., 62, M	Ext. larynx	X-ray	1952	Squamous ca.	?2 yr.	Right lung	Pain	x	..	..	Exploratory thoracotomy	1/54	Squamous ca., grade III	5/54, died of disease; culpability 2 yr.; "pain" in back undiagnosed
26	M. B., 58, M	Right lung	X-ray, HN2	10/53	Squamous ca., grade III	6 mo.	Ext. larynx	Hoarseness	..	..	x	X-ray	4/54	Squamous ca., grade III	8/54, no evidence of disease
27	D. B., 63, M	Ext. larynx	Radical neck dissection, total laryngectomy	1949	Squamous ca., grade II and neck nodes	4½ mo.	Left lung	Cough	x	x	..	X-ray	5/54	Epidermoid ca.	9/54, no evidence of disease
28	E. D., 62, M	Right lung	Radon seeds	5/54	Epidermoid ca. to periosteum of ribs	0	Ext. larynx	.....	..	..	x	X-ray and radon	5/54	Epidermoid ca., grade II, presumably adult Wilms' tumor	9/16/54, living with disease
29	G. K., 68, M	Int. larynx; vocal cord; neck nodes later	Cordectomy	1/48	Squamous ca. (early)	0	Lung	X-ray	x	x	..	Thoracotomy and x-ray	2/48	Epidermoid ca.	5/49, died of disease, 1 yr.
30	J. Z., 52, M	Int. larynx	X-ray, total laryngectomy	10/44	Squamous ca., grade II	3 mo.	Right lung	Cough, dyspnea	x	..	x	X-ray	9/47	Epidermoid ca., grade II	7/48, died of disease, 10 mo.

31	J. G., 80, M	Int. larynx	Excision	3/48	Squamous ca., grade II	0	Right lung	Cough, fever	x	x	x	Radium bronchoscopy	4/48	Epidermoid ca., grade II	4/54, died, 4 yr.
32	T. McC., 56, M	Int. larynx	Partial laryngectomy	4/48	Epidermoid ca., grade II	0	Right lung	Cough, hemoptysis	x	x	..	Right upper lobe and right middle lobe lobectomy	5/48	Epidermoid ca., grade III and nodes	11/48 died, ? chest negative
33	H. A., 41, M	Int. larynx	Laryngofissure	1944	Epidermoid ca.	5 yr.	Left lung	Cough, pain; hemoptysis	x	x	..	HN_2	4/49	Squamous ca.	6/49, died of disease
34	J. M., 84, M	Int. larynx	X-ray	11/50	Squamous ca., grade II	0	Left lung	Hemoptysis	x	x	x	X-ray	1/51	? Squamous type	8/51, died of disease
35	W. P. N., 62, M	Int. larynx	Laryngectomy	1/48	Squamous ca., grade II	46 mo.	Left lung	X-ray	x	..	..	Left radical pneumonectomy	11/51	Epidermoid ca., nodes negative	9/54, no evidence of disease, also has Boeck's sarcoidosis
36	M. J. C., 42, M	Int. larynx	Neck dissection and seeds	2/48	Squamous ca., grade II; metastasis 2 levels	4 yr.	Right lung	Cough, pain	x	x	x	Exploratory thoracotomy, seeds, x-ray	5/52	Epidermoid ca., grade II	6/53, died of disease, culpability, antibiotics
37	M. M., 35, F	Bronchogenic neck cyst, ca.	X-ray	10/34	Squamous ca. in cyst	4 yr.	Right lung	Cough, pain	..	..	x	None	3/38	Squamous ca., grade I	6/38, died of disease, too much disease for treatment
38	C. P., 64, M	Right lung	Simple pneumonectomy	6/48	Squamous ca., grade II; vein invasion	4 yr.	Left supraclavicular Hodgkin's disease node	Chance	..	..	x	X-ray	11/52	Hodgkin's granuloma	8/54, no evidence of disease, 2 yr.
39	H. L., 49, M	Chronic lymphatic leukemia	P-32 and x-ray	1/51	Chronic lymphatic leukemia	0	Right lung	Cough	x	x	x Nodes	Radon and x-ray	6/51	Mucous gland ca.; metastases to mediastinum and trachea	Lost to follow-up
40	J. G., 40, M	Neck	X-ray	1946–1951	Hodgkin's disease	6 yr.	Right lung	Abscess	x	..	x	X-ray and drainage	6/52	Anaplastic epidermoid ca.	6/52, died
41	C. G., 65, F	Leukemia	X-ray ,P-32	1945	Lymphatic leukemia	5 mo.	Lung	Cough	x	x	..	X-ray	6/49	Bronchogenic ca.	3/50, died of disease, 9 mo.
42	H. H., 62, M	Right lung	Simple pneumonectomy	1/48	Bronchogenic ca.	4½ mo.	Descending colon	Right lower quadrant pain	Exploratory laparotomy			Left hemicolectomy	8/52	Adenocarcinoma, Duke's C, metastasis to level 2	8/54, no evidence of disease, 2 yr.

TABLE III (*Continued*)

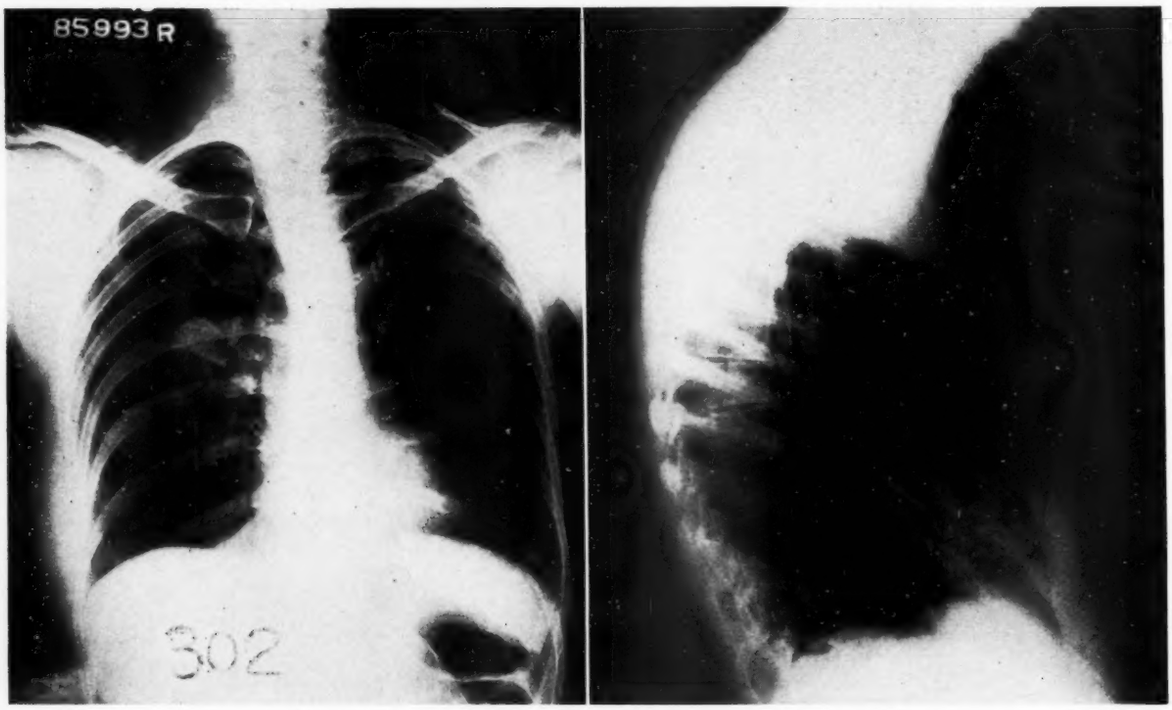
Case No.	Patient, Age (Yr.) and Sex	Site of First Primary Tumor	Method of Treatment	Date Treated	Pathology	Time Interval	Site of Secondary Primary Tumor	First Symptom	Preoperative Diagnosis			Method of Treatment	Date Treated	Pathology	Follow-up
									X-ray	Cytology	Biopsy				
43	G. S., 62, M	Colon	Excision	2/43	Adenocarcinoma	5½ yr.	Right lung	Cough, fever	x	x	x	X-ray, HN2	8/48	Spindle cell epidermoid alveolar ca. with widespread metastases	Died; autopsy, widespread metastases from ca. lung
44	J. H., 63, M	Rectum	Abdominoperineal resection	1937	Adenocarcinoma, gr. II	10 yr.	Lung	Cough	x	x	..	X-ray	1948	Squamous ca., grade II	1948, died of disease
45	W. H., 54, M	Rectum	Abdominoperineal resection	1937	Adenocarcinoma, grade II; nodes clear	10 yr.	Left lung	Hemoptysis	x	x	..	Left pneumonectomy	7/49	Epidermoid ca., bronchogenic ca.	9/54, no evidence of disease, 4 yr., 10 mo.
46	G. S., 55, M	Descending colon	Resection primary anastomosis	12/46	Adenocarcinoma, grade III, Duke's A	4½ yr.	Right lung	X-ray	x	..	..	Right radical pneumonectomy	5/51	Epidermoid ca., grade III; nodes negative	6/54, no evidence of disease, 3 yr., 1 mo.
47	W. M., 57, M	Right testicle	Excision, x-ray	1929	Embryonic cell	18 yr.	Left lung	X-ray	x	..	x Asp.	Exploratory thoracotomy	8/47	Ca. consistent with lung primary	Died of disease, no autopsy
48	L. S., 60, M	Testicle	X-ray, orchiectomy	1935	Teratoma	15 yr.	Right lung	X-ray	x	x	..	X-ray	5/50	Squamous ca.	12/50, died of disease, 7 mo.
49	A. B., 71, M	Bladder	Resection	1941	Epidermoid papilloma, grade I	2 mo.	Lung	Hemoptysis	..	..	x	Radon	12/42	Bronchogenic ca., grade II	12/43, died of uremia, 1 yr.
50	F. K., 67, M	Bladder	Transurethral resection	2/52	? ca., grade I papilloma	0	.....	Dyspnea	x	x	..	None	.....	.....	12/52, died of disease; lung ca. established by cytology of sputum alone (class III)
51	C. S., 66, M	Left lung	Died during preoperative work-up	.....	Epidermoid ca.	0	Bladder	Red blood cells in urine	..	..	..	None	.....	Epidermoid ca.	3/52, autopsy; chance finding in bladder
52	E. H., 56, M	Renal pelvis	Nephrectomy	7/47	Epidermoid ca.	0	Left lung	Hemoptysis	..	..	x Asp.	Pneumonectomy	12/46	Epidermoid ca., grade II; nodes clear	12/47, died of disease, 5 mo.

53	G. P., 72, M	Left chest	X-ray	7/52	? epidermoid ca. or glandular	13 mo.	Kidney	Hematuria	x	..	..	Right nephrectomy	8/53	Epidermoid ca., grade II, of pelvis	6/54, living with disease
54	E. S., 58, F	Right lung	Gold seeds, Au-98; primary and chest wall resection 4/52	4/52	Epidermoid ca., grade III	.....	Left kidney	Abdominal discomfort	x	..	..	Left nephrectomy	3/53	Adenocarcinoma permeating renal vein	5/53, died at home
55	W. T., 54, M	Prostate	X-ray, stilbestrol	9/41	Ca. (asp. biopsy)	12 yr.	Left lung	Chest pain	x	..	..	Simple pneumonectomy	9/53	Epidermoid ca., grade III; metastasis to 1 bronchopulmonary node	5/54, no evidence of disease, 8 mo.
56	K. G., 63, F	Cervix	Radium, x-ray	1948	Papilloma, adenocarcinoma, endocervix	2 mo.	Right lung	X-ray	x	..	..	Right radical pneumonectomy	6/51	Terminal bronchiolar ca.	8/54, living with pelvic disease
57	E. B., 58, F	Breast	Radical mastectomy	1946	Infiltrating duct ca.	3 mo.	Left lung	Pain	x	..	x Asp.	Pneumonectomy	8/49	Bronchogenic epidermoid ca., grade III, and nodes	10/49, died of disease, 2 mo.
58	F. C., 66, F	Chest wall	Multiple excisions	1945, 1947, 1948	Fibrosarcoma	4 yr.	Right lung and diaphragm	Pain, weight loss	x met.	..	..	Right lower lobe lobectomy; seeds; diaphragm-chest wall x-ray	10/52	Spindle cell ca. not related to sarcoma	3/53, died of disease; culpability 4 yr., watching nodule in lung x-ray
59	J. C., 58, M	Right lung	None	2/54	Epidermoid ca. with metastases over-all	0	Common bile duct	Jaundice	..	..	..	.....	.....	Adenocarcinoma	Died of disease; chance finding at autopsy (gallbladder)
60	H. L., 42, M	Multiple skin	Multiple excisions and x-ray	1940–1951	Squamous ca., grade II	?	Right lung	Cough, hemoptysis	x	Failed	Failed	Right radical pneumonectomy	1/52	Epidermoid ca., grade III; negative nodes	No evidence of disease on autopsy; postoperative death
61	S. K., 67, M	Skin scrotum	Excision 6/49; right radical groin dissection	3/50	Epidermoid ca.	4 yr.	Right lung	Wheezing	x	Failed	..	X-ray	6/54	Oat-cell ca.	8/54, died of disease, autopsy
62	T. C., 72, M	Right ear	None	8/53	Squamous ca., grade I	3 mo.	Right lung	Cough	x	x	0	Exploratory thoracotomy and biopsy	12/53	? tuberculosis	3/54, died of disease

TABLE III (*Continued*)

Case No.	Patient, Age (Yr.) and Sex	Site of First Primary Tumor	Method of Treatment	Date Treated	Pathology	Time Interval	Site of Secondary Primary Tumor	First Symptom	Preoperative Diagnosis			Method of Treatment	Date Treated	Pathology	Follow-up
									X-ray	Cytology	Biopsy				
						Triple Primaries									
63	A. C., 40, F	(1) Breast (2) Sigmoid	(1) Radical mastectomy (2) Sigmoidectomy	5/41 9/49	Infiltrating duct ca. and nodes Adenocarcinoma, grade II; Duke's B	8 mo. 2 mo.	Lung	X-ray	x	x	..	Right upper lobe and right middle lobe lobectomy	11/49	Bronchogenic ca., bronchiolar	11/54, no evidence of disease, 5 yr.
64	P. C., 59, M	(1) Tongue (2) Ext. larynx	(1) Partial glossectomy (2) Radical neck dissection and laryngectomy	3/49 11/51	Epidermoid and adenocystic ca. Epidermoid ca.	2 yr.	Right lung	Hemoptysis	x	x	x	5/53 x-ray and seeds; exploratory thoracotomy	5/53	Epidermoid ca.	Died of disease, 13 mo.
						Basal Cells									
65	S. T., 30, M	Nose	Excision	3/34	Basal cell	0	Left lung	Cough, pain	x	..	x	X-ray	2/34	Adenocarcinoma	Suicide with disease, 2 yr.
66	S. C., 46, M	Skin of lip	Excision	1927	Basal cell	8 yr.	Bronchus	Cough, pain	x	..	x	X-ray	10/36	Epidermoid ca., grade II	12/36 died of disease, 2 mo.
67	O. M., 69, M	Right eyelid	X-ray and excision	1941	Basal cell	10 yr.	Left lung	Cough, weight loss	x	..	x	X-ray	12/51	Epidermoid ca.	Living with disease, 26 mo.
68	C. H., 77, M	Skin	X-ray	8/47	Basal cell	0	Lung	Pain	x	x	x	X-ray	8/47	Epidermoid ca.	Died of disease, 12/47
69	C. R., 52, M	Multiple	X-ray	6/47	Basal cell	0	Right lung	X-ray	x	..	..	Right upper lobe lobectomy	6/47	Bronchogenic ca., grade III; vein invasion; pleural involvement	Died of heart attack, 5 yr.
70	J. B., 59, M	Skin neck	Excision	11/47	Basal cell	1 yr.	Right lung	Cough, hemorrhage	x	x	..	Radical pneumonectomy	6/48	Squamous ca., grade III; metastasis to 2 nodes	At autopsy no evidence of ca.; cardiac failure 5 yr.

71	C. W., 67, M	Left eyelid	X-ray	12/48	Basal cell	0	Right lung	Pain	x	..	x	Pneumonectomy with chest wall resection	12/49	Malignant bronchial adenoma	Autopsy, malignant bronch. adenoma; metastasis to liver; pulmonary embolus 2 mo.
72	E. W., 56, M	Cheek	Excision	5/48	Basal cell	5 mo.	Right lung, left supraclavicular	Pain	x	..	x	Node excision	10/48	Squamous ca.	Died of disease, 5/49
73	R. McA., 68, M	Skin nose	Excision	8/48	Basal cell	0	Right lung	Hemoptysis	x	..	x	Pneumonectomy	7/48	Epidermoid ca., grade III	9/54, no evidence of disease, 6 yr.
74	V. H., 72, M	Left cheek	Excision	12/49	Basal cell	0	Right lung	Cough, pain	x	x	x	Pneumonectomy	7/48	Squamous ca., grade III	8/12/54, no evidence of disease, 6 yr.
75	F. F., 58, M	Nose	Excision	6/51	Basal cell	0	Left lung	Hoarseness	x	..	..	Exploratory thoracotomy, x-ray	5/50	Anaplastic ca.	10/52, died of disease, autopsy, 29 mo.
76	J. B., 66, M	Nose	X-ray	?1942	Basal cell	?8 yr.	Right lung	Cough, dyspnea	x	x	N.D.	Right radical pneumonectomy	3/50	Epidermoid ca., grade I	4/54, no evidence of disease, 4 yr.
77	R. K., 60, M	Skin	X-ray	1948	Basal cell	2 yr.	Lung	Cough	x	x	..	X-ray	2/50	Bronchogenic ca.	4/50, died of disease, 2 yr.
78	C. G., 71, M	Nose	Excision	3/53	Basal cell	0	Right lung	Cough, hemoptysis	x	x	x	X-ray	10/52	Epidermoid ca., grade III, anaplastic	Died of disease, 9 mo.
79	F. B., 59, M	Mastoid	Radical mastoidectomy	9/53	Basal cell	0	Left lung	X-ray	x	x	Failed	X-ray	11/53	Epidermoid ca., grade II	1/54, died of disease, 2 mo.
80	F. B., 39, M	Nose	Excision	6/46	Basal cell	7 yr.	Right lung	X-ray	x	Failed	..	Exploratory thoracotomy with radon and x-ray	12/53	Anaplastic bronchogenic ca.	9/8/54, living with disease; polyp in rectum, 9 mo.
81	J. H., 62, M	Skin axilla	Excision	12/43	Basal cell	0	Lung	Cough	x	..	x	X-ray	12/43	Metastatic ca.	3/44, died of disease, 3 mo.



4A 4B

FIG. 4. Case 63. A and B, triple primary, postero-anterior and lateral views. Chest roentgenograms showing opacity in right upper and middle lobes.

Four cases will be described in some detail:

As evidence of the value of aggressive therapy the following case report of a woman who had separate carcinoma of the breast, colon and lung is of interest:

CASE 63. A thirty-nine year old woman had a right radical mastectomy in May, 1941, with a pathologic report of infiltrating duct carcinoma with metastases to axillary lymph nodes at all levels. Eight years and four months later adenocarcinoma, Grade II, Duke's B of the transverse colon was removed by anterior resection. Two months later a shadow in her right lung was noted on a routine roentgenogram. (Fig. 4.) She was bronchoscoped and the cytology of the bronchial washings showed the presence of cancer without definition as to histologic type. Stereoscopic views of the lungs and x-rays of her skeletal system as well as other detailed laboratory studies failed to reveal any evidence of spread from the breast and colon cancers. In November, 1949, exploratory thoracotomy was performed, and in the absence of other nodules, this peripherally placed tumor was removed by right upper and middle lobe radical lobectomy. (Fig. 5.) The histologic diagnosis was terminal bronchiolar carcinoma. (Fig. 6C.) All peribronchial and mediastinal lymph nodes were negative. This patient is alive without evidence of disease five years after her last procedure.

CASE 19. This sixty-four year old man was first seen on February 17, 1949, with a three-month history of hoarseness, for which he received eighteen penicillin injections. On laryngoscopic examination there was a large, fungating, pedunculated lesion which was 3 cm. wide and 5.5 cm. in length, rising on the right side of the extrinsic larynx, invading the epiglottis and right vocal cord. A routine chest film showed a shadow in the left lung field, and it was suggested by the radiologist that this was compatible with primary carcinoma of the lung. (Fig. 7.) Aspiration biopsy of the left lung was performed after cytology failed to yield definitive cellular types. It was decided that the lung cancer was probably the more malignant of the two, and on March 29, 1949, left radical pneumonectomy was performed. (Fig. 8.) The pathologic diagnosis was squamous carcinoma grade II, mediastinal lymph nodes clear. A gross description of the lesion showed that the cancer had its origin from the major bronchus to the lower lobe, and the mass meas-

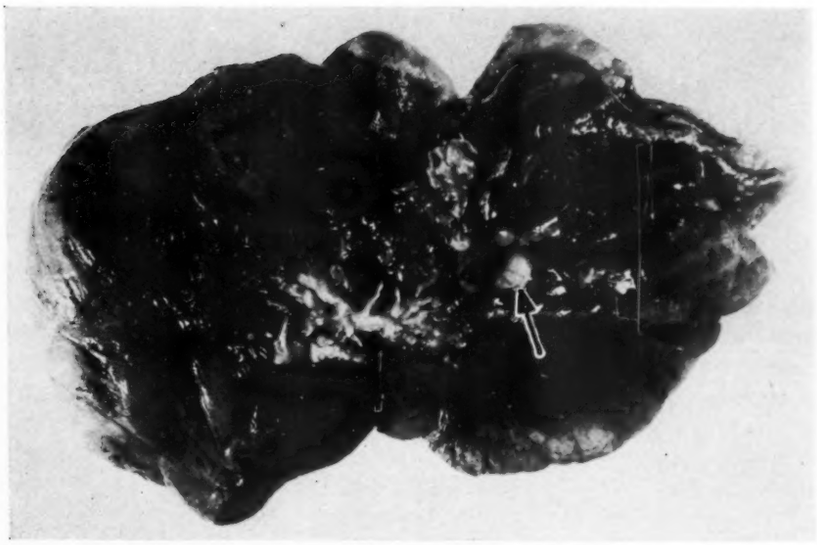
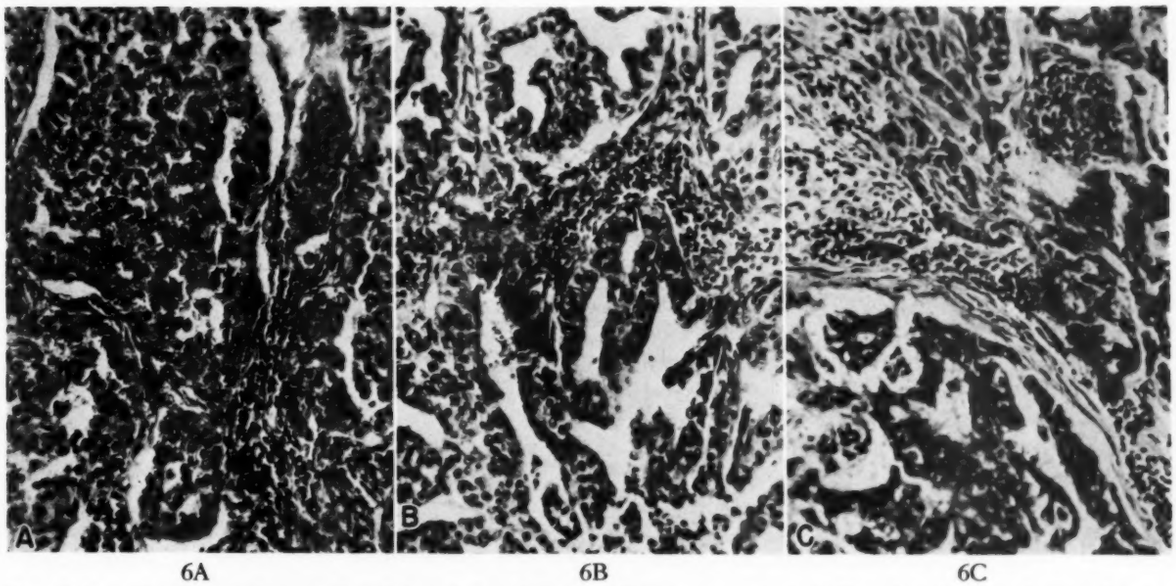


FIG. 5. Case 63. Triple primary. Right upper and midle lobes containing lesion (arrow).

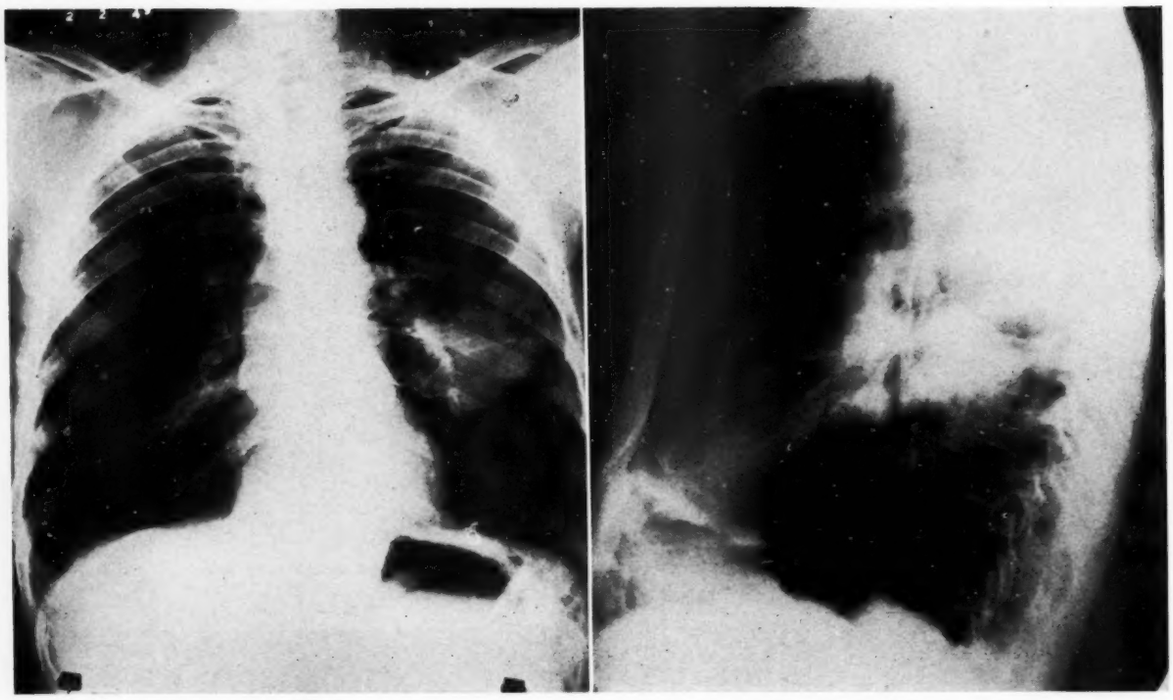


6A 6B 6C

FIG. 6. Case 63. Photomicrographs of the triple primary malignant tumors. A, infiltrating duct carcinoma, breast; B, adenocarcinoma, grade II, of rectum; C, bronchogenic carcinoma, terminal, bronchiolar type.

ured 7 by 4 cm. At the conclusion of the pneumonectomy prophylactic tracheostomy was performed. On May 11, 1949, six weeks later, total laryngectomy was performed and the pathologic specimen was squamous carcinoma grade II. (Fig. 9.) The patient recovered from this procedure without difficulty, and was discharged from the hospital two weeks later. Since that time he has returned to work and was last seen on August 26, 1954, over five years after his two operative procedures, without any evidence of disease.

Comment. This patient is the first in whom synchronous cancer of the extrinsic larynx and the lung existed. The choice of treating the more malignant tumor first resulted in radical pneumonectomy, at the conclusion of which procedure tracheostomy was performed. His uneventful recovery permitted the second operation within a six-week period, and he has been without evidence of disease for five years and nine months. If it had been assumed that the shadow in the lung were metastasis, x-ray therapy would have been administered to both



7A 7B

FIG. 7. Case 19. A and B, postero-anterior and lateral chest roentgenograms showing shadow in left mid-lung field posteriorly placed.

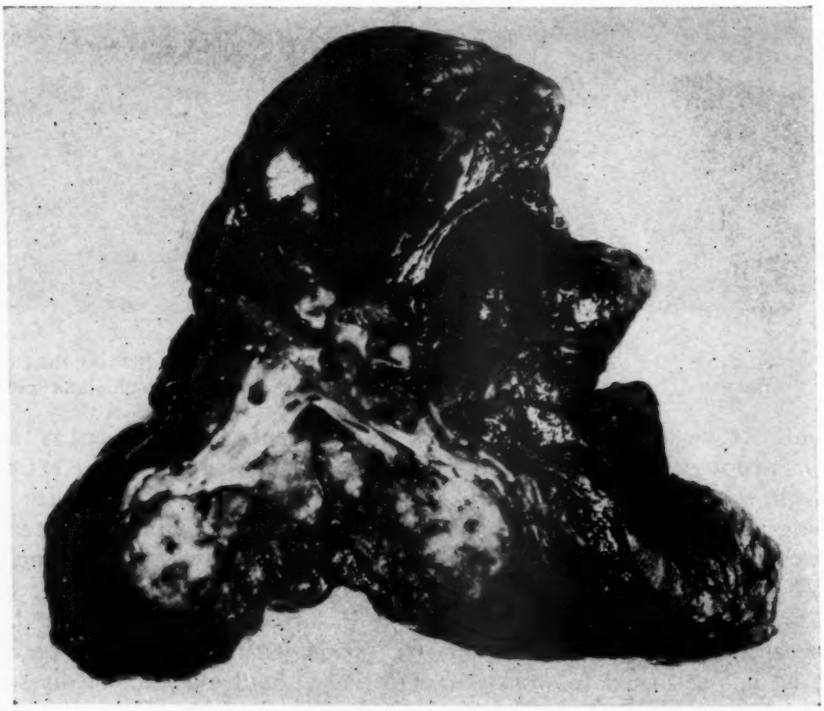


FIG. 8. Case 19. Specimen of left lung showing carcinoma in left lower lobe.

sites, and one doubts that survival for this length of time would have been possible.

CASE 41. The patient was a 65-year old white woman who was first seen on September 29, 1948, presenting a history of lymphatic leukemia of five years' duration. She had been treated elsewhere for the disease by roentgen irradiation, radioactive phosphorus and urethane. On examination, there were generalized adenopathy and hepatosplenomegaly. White blood count was over 200,000 with 92 per cent lymphocytes. She had no pulmonary complaints, but a submitted chest roentgenogram taken four months previously showed a 6 cm. opacity in the right lower lung field. This was reported by the radiologist as "consistent with bronchiogenic carcinoma." Bronchoscopy did not visualize the tumor. A sputum specimen was reported as Class v, "Shows large masses of lymphocytes and also clusters of neoplastic cells suggestive of a malignant lung tumor, adenocarcinoma in type." Roentgen ray therapy to the lung lesion was begun on May 6, 1949, and the patient was given 3,000 r to each of two chest portals, anterior and posterior, using the 1,000 kv. machine. She remained asymptomatic until February 9, 1950, when she complained of marked weakness, nasal hemorrhages, and axillary and inguinal lymph node enlargement developed. ACTH was administered without avail. She died on March 20, 1950. At autopsy the diagnosis of terminal alveolar adenocarcinoma of the right lower lobe of the lung, metastatic to liver, was revealed, together with diffuse evidences of lymphatic leukemia.

Comment. In this instance radiation therapy was selected as the method of choice for the lung lesion because the hemorrhagic propensity of patients with leukemia precluded surgical intervention.

CASE 45. This patient was a fifty-four year old white man who first came to Memorial Hospital on July 19, 1940, with a complaint of rectal bleeding of eight months' duration. Biopsy of a rectosigmoid lesion, 12.5 cm. from the anal margin, was reported to be adenocarcinoma, grade II. On October 24, 1940, a one-stage, combined abdominoperineal resection was performed. On subsequent follow-up visits the patient was reported to be well, until May 2, 1949, when he complained of slight cough and bloody sputum. Roentgenogram of the chest indicated the possibility of early bronchiogenic

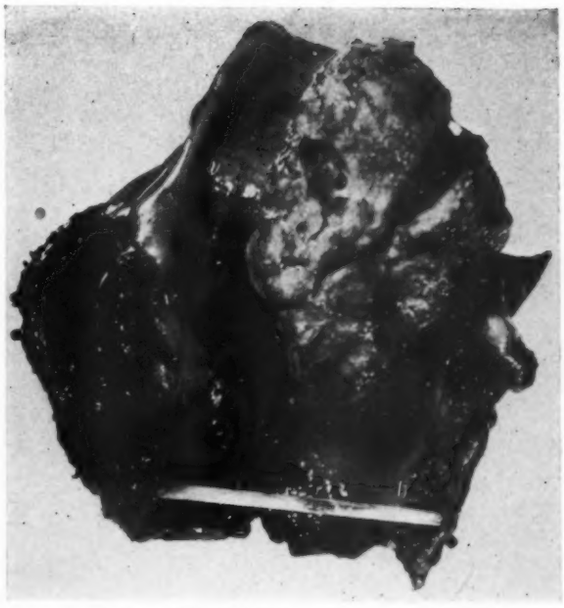


FIG. 9. Case 19. Total laryngectomy specimen (posterior view, opened) showing carcinoma of extrinsic larynx in patient who had radical pneumonectomy six weeks previously. (Fig. 8.) He is alive and well without evidence of disease over five years later.

carcinoma. Bronchoscopy had revealed no apparent abnormality. Papanicolaou studies of bronchial washings were reported as class v, "Conclusive evidence of a squamous carcinoma of the lung." On July 15, 1949, at exploratory thoracotomy, a tumor mass was found in the apex of the left lower lobe, measuring about 4 cm. in diameter, and extending across the interlobar fissure to the left upper lobe. Left radical pneumonectomy was performed and the specimen was reported as bronchiogenic squamous carcinoma—mediastinal lymph nodes clear. The patient had an uneventful recovery and was without evidence of disease five years and six months later.

Comment. The development of metachronous lesions, in this case of the rectum and lung, was separated by nine years, and a preoperative diagnosis of a new primary pulmonary cancer was derived from roentgenograms and bronchial cytologic studies.

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Bronchiolar Carcinoma

(ALVEOLAR CELL TUMOR—PULMONARY ADENOMATOSIS)

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BRONCHIOLAR carcinoma is a rather uncommon but highly important type of pulmonary malignancy. This tumor also has been referred to as alveolar cell carcinoma, alveolar cell tumor, pulmonary adenomatosis and by an almost endless variety of other descriptive titles.[1] Some have questioned whether all of the lesions reported under the numerous synonymous or related terms represent variants of a single entity or whether they include two or more distinct though similar tumors. The best evidence appears to indicate that all of the lesions in this group represent the same neoplasm which may vary considerably in its histologic picture and clinical behavior.[2] It was formerly believed that this tumor was invariably bilateral in distribution, that the lesions were always widespread in extent and that patients with this disease were faced with a hopeless outlook. Fortunately, modern advances in diagnostic and therapeutic technics have rather clearly established the fact that this dismal prospect does not necessarily prevail. On the contrary, recent experience indicates that this tumor is frequently if not always localized in its early stage and that resection at this time may offer a better prognosis than with any other lung cancer. Three brief case reports* serve to illustrate certain features of this disease.

CASE REPORTS

CASE 1. J. J. M. (Reg. No. 109054), a thirty-seven year old white man, was admitted to the U. S. Naval Hospital, St. Albans, New York, in November, 1949, because a routine chest x-ray had shown a discrete solitary lesion in the left upper lung field. He complained of a mild non-productive cough of six or seven months' duration, which he attributed to smoking. He also mentioned a slight ache in the left anterior chest which had been present for an indefinite period of time, but at least for many months. His present and past medical history was otherwise negative. The family history was non-contributory. Complete physical examination revealed no abnormal findings. The patient did not appear to be ill. Routine laboratory studies gave results within the normal range. The tuberculin skin test was positive in the second strength. Postero-anterior and left lateral chest roentgenograms revealed a round, homogeneous, sharply circumscribed lesion measuring 2 cm. in diameter situated in the anterior segment of the left upper lobe. (Fig. 1.) Postero-anterior and lateral tomograms confirmed these findings. In addition, some observers thought that a fleck of calcific density could be seen in the center of the lesion on the tomograms. Bronchoscopy showed no abnormalities of the tracheobronchial tree. The bronchial aspirate was negative on smear for acid-fast bacilli. Cultures of the aspirate planted at this time were subsequently reported as negative for tubercle bacilli. Cytologic studies of the sputum and bronchial aspirate were not done. Ten days after admission left thoracotomy was performed and a moderately firm spherical lesion was removed by excisional biopsy from the anterior segment of the left upper lobe. On sectioning, this mass did not present the gross appearance of a chronic pulmonary granuloma but suggested a tumor. Immediate frozen sections were made which showed bronchiolar carcinoma. (Fig. 2.) Careful inspection and palpation of the left lung revealed no other lesion. There were no enlarged or firm mediastinal lymph nodes. Left upper lobectomy was performed. The patient's postoperative course was uneventful. His chest x-rays approximately three years postopera-

* These cases have all been reported in abstract form.[2]

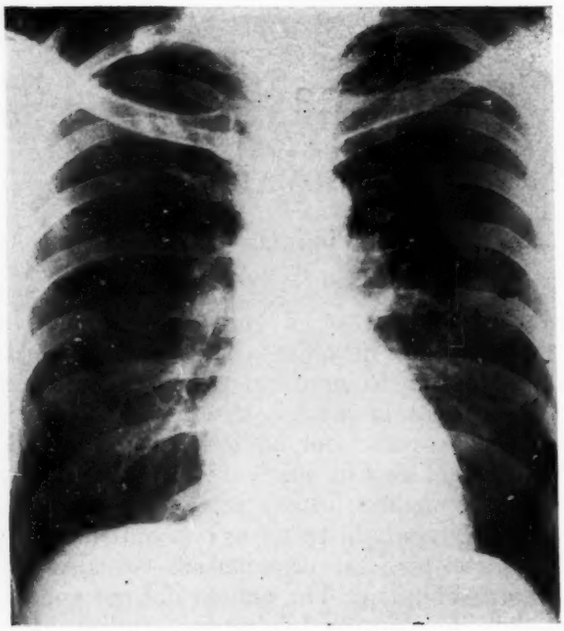

FIG. 1. Case 1. Admission chest roentgenogram showing sharply circumscribed ovoid lesion 2 cm. in diameter at the level of the third left anterior interspace. (From Storey et al., *J. Thoracic Surg.*, 26: 331, 1953.)

FIG. 2. Case 1. Histologic section of the resected tumor showing the typical picture of bronchiolar carcinoma. × 280. (Armed Forces Institute of Pathology, Washington, D. C.)

tively (Fig. 3) revealed no pathologic condition. At the present time, almost five years after resection, he remains clinically well. His chest x-rays are essentially negative and he is on active duty in the Navy.

Comment. Prompt resection of this patient's lesion appears to have paid dividends. Time was not wasted in intensive diagnostic measures that would probably have proved unrewarding. Results of sputum cultures were not awaited. The cultures are usually negative

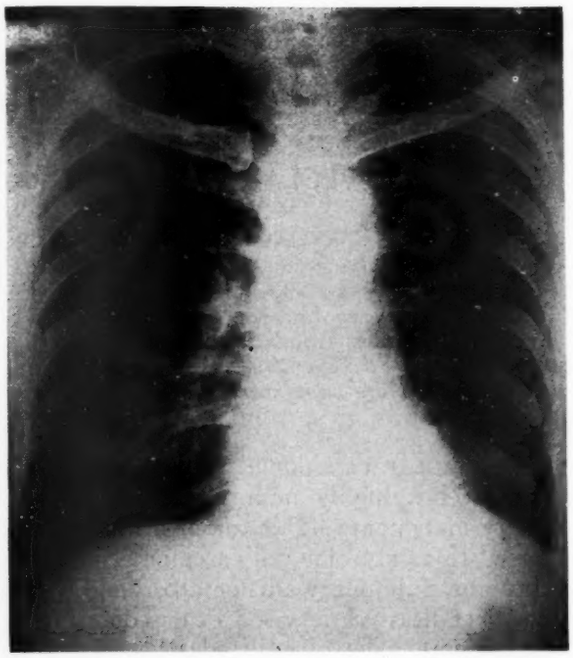

FIG. 3. Case 1. Chest roentgenogram made three years after left upper lobe lobectomy. There is no evidence of residual or recurrent disease.

in lesions of this type even when they are of tuberculous origin. Much can be said in favor of an aggressive policy with early excisional surgery in patients presenting a solitary peripheral pulmonary nodule.

CASE II. J. N. H. (Reg. No. 116208) was admitted to the U. S. Naval Hospital, St. Albans, in October, 1950, because a routine chest x-ray taken at the time of induction into the service had shown a rounded lesion 2 cm. in diameter in the right upper lung field. (Fig. 4.) The patient had had a pre-employment chest x-ray twenty months previously which was interpreted as negative, although on review a round lesion 2 cm. in diameter (Fig. 5) could be clearly identified at the same site as the lesion shown on his induction film. On admission the patient complained of a burning sensation beneath the right scapula of four months' duration, low back pain radiating to the right leg for about four months, and a dry cough for two or three months. He did not appear to be ill. His past medical history and family history revealed nothing noteworthy. Physical examination was negative and routine laboratory studies gave results within normal limits. Nothing abnormal was seen on bronchoscopy. The bronchial aspirate and numerous smears and cultures of the sputum and

gastric contents were negative for tubercle bacilli. Papanicolaou preparations of the sputum were suspicious of malignancy (class III) on several occasions. The tuberculin skin test was positive in the weakest dilution. Chest roentgenograms one month after admission showed a spread in the vicinity of the original lesion, a halo of fine nodular lesions measuring 1 or 2 mm. in diameter having made their appearance. By December, 1950, a month after this, these lesions were more pronounced and similar miliary nodules could be seen in the opposite lung as well as in all lobes of the right lung. The clinical diagnosis of miliary tuberculosis was made and the patient was started on therapeutic doses of streptomycin and PAS, but these drugs failed to alter the course of his disease. In January, 1951, he was found to have a pericardial effusion. (Fig. 6.) Pericardiocentesis was performed on two occasions, 800 and 500 cc. of hemorrhagic fluid being removed on the two taps. Cytologic study of this fluid revealed malignant cells of an unidentified type. Late in January a lung biopsy was performed through a small right anterior intercostal incision. Histologic examination of the surgical specimen showed bronchiolar carcinoma. The patient's pulmonary lesions showed steady progression. (Fig. 7.) He became increasingly short of breath and died of respiratory insufficiency early in March, 1951. Postmortem examination showed that widespread bronchiolar carcinoma involved all lobes of both lungs with metastases to the heart, liver, kidneys and spine.

Comment. This patient's lesion was unfortunately missed at the time of his first chest x-ray examination. When the peripheral nodule was noted on his chest roentgenograms twenty months later, the lesion remained stable and prompt excision at that time may have afforded the chance of a cure. The belief that the lesion was tuberculous in nature resulted in procrastination while an intensive effort was made to establish the diagnosis of pulmonary tuberculosis. By the time the correct diagnosis was established widespread dissemination of the neoplasm had occurred, making the prognosis hopeless.

CASE III. N. L. F. (Reg. No. 248326) was admitted to the U. S. Naval Hospital, Portsmouth, Virginia, on March 24, 1952, in the fifth month of her first pregnancy, complaining of pain in the left chest. This was described as a "pulling sensation" which was aggravated by deep breathing, coughing or exertion. These symptoms began two months previously and had gradually increased in severity. Her past medical history, systemic review and family history were non-contributory. Physical examination showed the findings consistent with an intrauterine pregnancy of five months' duration but was otherwise unremarkable. Routine laboratory studies showed no abnormalities. A chest x-ray taken just before admission showed multiple miliary soft tissue densities throughout both lung fields which the radiologist considered to be due to vascular shadows viewed axially. Repeat chest roentgenograms in April, 1952, showed that these lesions had increased in number and size, and it was apparent that they represented parenchymal involvement and not blood vessels. (Fig. 8.) The sputum and gastric washings were repeatedly negative on culture for acid-fast bacilli. Subsequent chest x-rays taken at intervals of every few weeks showed a progressive increase in the pulmonary lesions which involved all lobes of both lungs. (Fig. 9.) Meanwhile, her pregnancy progressed normally and a healthy male infant was delivered spontaneously in August, 1952. Following delivery the patient suffered increasing chest pain and shortness of breath. Her vital capacity progressively diminished until November, 1952, when it was 1.5 L. A left thoracotomy with lung biopsy was performed in November, 1952, and histologic examination of the surgical specimen was interpreted as showing "pulmonary adenomatosis." (Fig. 10.) She withstood the operative procedure well but her downhill course continued; she became markedly dyspneic and cachectic, and died on July 4, 1953, of pulmonary insufficiency. Complete postmortem examination showed extremely extensive tumor involvement of all lobes of both lungs. There were no metastases to the mediastinal nodes or other thoracic structures and no distant metastases were found at that time. Because the histologic characteristics of the pulmonary lesions lacked many of the features commonly associated with malignancy and no local or distant metastases were discovered, the diagnosis of pulmonary adenomatosis was established.

Comment. This case illustrates the vagaries of this disease. The patient was a Navy nurse and had had chest x-rays yearly. In spite of this her lesions were bilateral and extensive at

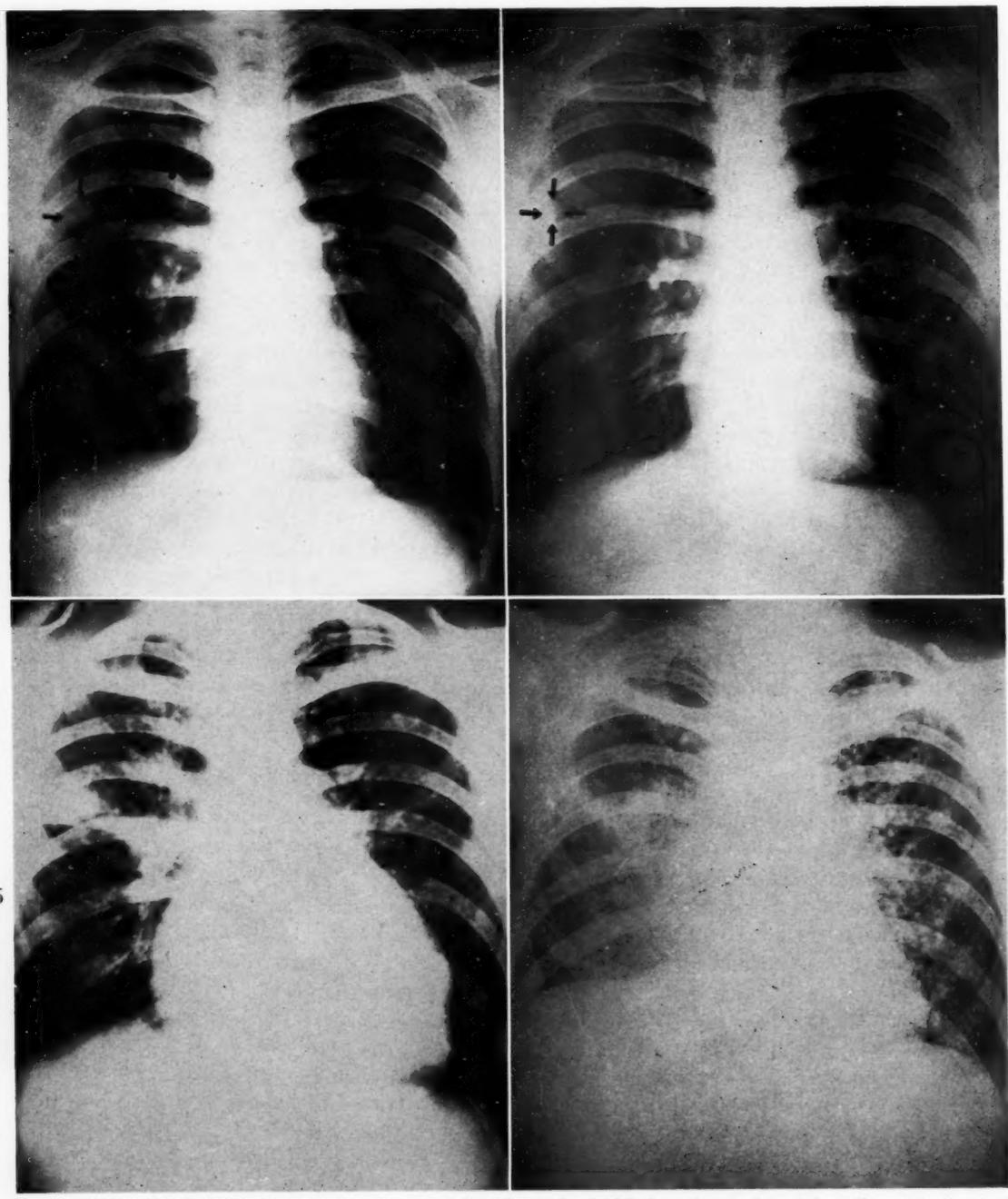

FIG. 4. Case 11. Admission chest roentgenogram showing spherical lesion situated peripherally at the level of the third right anterior interspace.

FIG. 5. Same case. Chest roentgenogram made sixteen months prior to admission. The lesion seen on the admission film was clearly visible in this x-ray and has not changed appreciably in size in the interim. (From Storey et al., *J. Thoracic Surg.*, 26: 331, 1953.[2])

FIG. 6. Same case. All lobes of both lungs are now involved by discrete nodular lesions and a large pericardial effusion has developed.

FIG. 7. Same case. The patient's lesions have increased in size and number, and there is diffuse consolidation adjacent to the right border of the heart. (From Storey et al., *J. Thoracic Surg.*, 26: 331, 1953.[2])

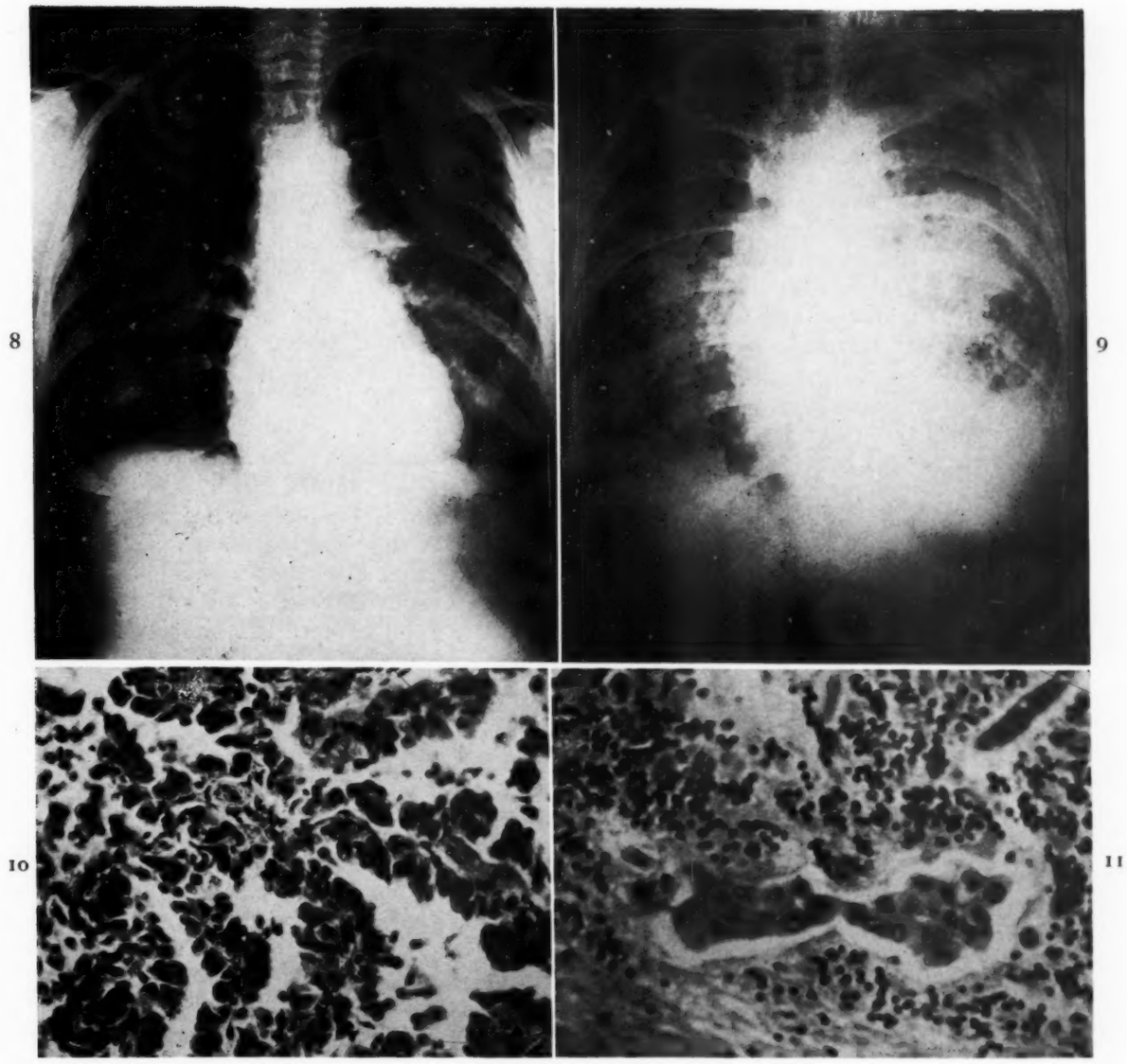

FIG. 8. Case III. Chest roentgenograms made about one month after admission showing many fine discrete nodular lesions involving all lobes of both lungs, more prominent in the lower one-half of the lung fields.

FIG. 9. Same case. Chest x-ray made about nine months after admission showing a striking increase in the lesions.

FIG. 10. Same case. Histologic section of lung biopsy specimen showing the typical picture of bronchiolar carcinoma. × 280. (Armed Forces Institute of Pathology, Washington, D. C.)

FIG. 11. Same case. Histologic section which shows a metastatic tumor focus in the cerebellum. × 300.

the time of their discovery. This case also illustrates an important point pertinent to the argument concerning benign pulmonary adenomatosis versus malignant bronchiolar carcinoma. At the time of lung biopsy the diagnosis of pulmonary adenomatosis was established. The diagnosis was confirmed at postmortem examination when no metastatic lesions were found in the mediastinal nodes or elsewhere. However, in preparation for a Clinical-Pathological Conference over a year later, new sections were made from all of the vital organs and small nests of neoplastic cells were seen along the stalk and in the capsule of the anterior lobe of the pituitary, in the cerebellum (Fig. 11), in the pia arachnoid, and in one section through the lenticular nucleus. The cellular arrangement was similar to that

present in the primary pulmonary lesions. Some of the foci showed papillary formations. Some of the tumor cells appeared to be ciliated.

REMARKS

Definition. We have suggested that the diagnosis of "bronchiolar carcinoma" be limited to those tumors which meet the following criteria: (1) a tumor characterized by alveoli lined by epithelial cells of columnar or cuboidal type with eosinophilic cytoplasm and basally placed nuclei; (2) a new growth which does not destroy the pulmonary architecture; (3) one in which there is no intrinsic tumor of a bronchus; and (4) in which there is *no evidence* of primary adenocarcinoma elsewhere in the body.

Histogenesis. The multiplicity of nomenclature applied to this tumor appears to be but a reflection of the lack of precise knowledge as to its histogenesis. In this connection there are two definite schools of thought. One holds that the alveoli possess an epithelial lining and that the tumor takes origin from the lining cells at this site;[3] the other contends that the alveoli are not lined by epithelium and that the lesion arises from the basal cells of the bronchioles.[4] The preponderance of evidence suggests the bronchioles as the most likely site of origin and this writer holds to that belief for the following reasons: (1) There is considerable histologic evidence which indicates that the alveoli are lined by mesenchymal rather than epithelial cells. (2) Carcinomas, by definition, are invariably of epithelial origin. (3) Bronchioles are clearly lined by epithelium and therefore *could* give rise to these cancers. (4) Histologically, the tumor cells resemble the lining cells of the normal bronchiole. (5) Microscopically, these lesions can be seen extending from bronchioles to alveoli. Two recent studies emphasize strongly the relative unimportance of the arguments as to the origin of this tumor. First, Brachet[5] has questioned the doctrine of absolute specificity of the germ layers, stating that they actually possess pluripotentiality; Their actual potentiality represents what they normally become, their total potentiality what they are capable of forming under diverse natural or experimental influences. Second, Waddell's[6] recent observations suggest that the bronchiolar epithelium itself may be of mesodermal origin. Clinically, the important fact is that these tumors arise *peripherally* and whether they begin primarily in the bronchioles or the alveoli is chiefly a matter of academic interest.

Etiology. The cause of bronchiolar carcinoma is unknown. The striking morphologic resemblance of this cancer in man to jaagsiekte, an infectious disease in sheep, has frequently been pointed out. It is believed that jaagsiekte is due to a virus, since the disease is easily transmitted by housing infected sheep together with healthy sheep. Sheep affected with this disorder have severe pulmonary symptoms with marked watery nasal discharges.[7] Histologically, the lesions seen in jaagsiekte are composed of alveoli lined by a regular layer of non-ciliated high cuboidal epithelium, often papillary in nature, with prominent interstitial fibrosis. Despite its clinical and histologic similarity to jaagsiekte, there is no evidence to indicate that bronchiolar carcinoma in man is an infectious disease. Efforts to transmit the disease from man to laboratory animals have been unsuccessful. It is true, however, that a few reported cases of human bronchiolar carcinoma have been exposed to sheep ill with a pulmonary disorder, but this is a marked exception rather than the rule. Certain chemical carcinogenic agents such as urethane and dibenzanthracene have produced lung cancers in mice, and the histologic structure of these induced tumors is similar to bronchiolar carcinoma as seen in man. It has not been possible, however, to establish a close etiologic relationship between any of the common irritants and bronchiolar carcinoma.

Pathology. Gross: bronchiolar carcinoma consistently arises in the periphery of the lung. It may present as a solitary tumor or as discrete multiple nodules varying in size from 1 or 2 millimeters to several centimeters in diameter. These nodules may coalesce, giving rise to a solid tumor of considerable size which bears a striking resemblance to the stage of hepatization of lobar pneumonia. The cut surface of the tumor varies from grey-tan to yellow-brown and is moderately firm. Mucus often exudes from the cut surface. Cavities are seen rarely. Atelectasis of a major degree is distinctly uncommon, but focal atelectasis is seen frequently. Thorough search of the entire bronchial tree will fail to reveal a primary lesion in the bronchi. When the tumor nodules are subpleural in location, they present as slightly raised umbilicated masses. A pleural effusion

is not uncommon, and when present it is often serosanguineous in character.

Microscopic: Histologically the tumor is composed of alveoli which are lined by cells which are usually of the tall columnar type but they may be low columnar or high cuboidal. The cytoplasm is esoinophilic. The nuclei are round or oval and are located basally. Although the tumor cells are almost invariably nonciliated, in a few cases ciliated neoplastic cells have been seen. The pulmonary architecture is almost never destroyed, the tumor cells appearing to line the lumens of the alveoli and terminal bronchioles. While they are usually well differentiated without anaplastic features, more malignant tumor cells are encountered occasionally and the histologic picture has been found to vary from case to case and even in different portions of the same tumor. The tumor cells frequently form papillary projections within the alveoli and these papillary projections tend to desquamate into the alveoli. The cells of this new growth usually produce mucin although this is by no means an invariable feature. Invasion of the pulmonary lymphatics can be demonstrated in sections from over 50 per cent of the cases. Small nests of tumor cells are conspicuous in the perivascular lymphatics. Clusters of tumor cells are often found lying in the alveolar spaces in the tumor-bearing area as well as in distant portions of the bronchial tree. We have reviewed the slides from many cases originally diagnosed as pulmonary adenomatosis as well as a large number of histologic sections from tumors which were diagnosed primarily as bronchiolar or alveolar cell carcinoma, and no essential differences in the histologic picture have been found that would distinguish one from the other. Furthermore, those diagnosed as pulmonary adenomatosis frequently were shown to metastasize within the lung, to lymph nodes and to other organs. For this reason it seems clear that the term "adenomatosis," denoting a benign lesion, is no longer tenable and that all of these neoplasms should be classified as bronchiolar carcinoma.

CLINICAL FEATURES

Incidence. It has been estimated that this tumor constitutes between 1½ and 5 per cent of all lung cancers, and it appears that the latter figure is more nearly correct. There is strong reason to believe that these tumors are frequently reported as peripheral adenncarcinoma. This tumor exhibits no racial predilection. It occurs with about equal frequency in men and in women. The age incidence coincides with the so-called "cancer age." The average age of 218 patients recently reviewed[2] was fifty-four years, and 85 per cent of patients fell in the age group between thirty and seventy years. Thus the age incidence in this neoplasm does not differ materially from that of bronchial cancer.

Symptoms. The most common symptoms are cough, sputum production, dyspnea, chest pain, weight loss, hemoptysis, weakness, fever, anorexia and pain other than chest pain, in that order. It is noteworthy that 7 per cent of the reported cases had no symptoms and represented accidental x-ray discoveries. The character and degree of the cough in patients with this disorder is highly variable. It is usually not of the harassing type and is commonly proportionate to the amount of sputum production. These patients commonly produce clear, frothy, watery sputum which becomes purulent in character only when there is a complicating secondary infection. It has often been stated that this disease is characterized by the production of huge amounts of sputum, but this is *not* necessarily the case. In a series of 218 patients it was found that 17 per cent produced no sputum and an additional 56 per cent raised less than 3 ounces daily. Hence only 27 per cent of the patients raise really large amounts of sputum. Hemoptysis, frequently small in amount, is fairly common in patients with this tumor. Approximately one-third of them will show hemoptysis and it is not rare for this to be the initial symptom.

Duration of Symptoms. Bronchiolar carcinoma is most often a slowly progressive chronic pulmonary disease which is not debilitating until late in its course; it gives rise to a remarkably few systemic symptoms and usually kills by the sheer extent of the pulmonary involvement. Review of a large series of cases indicates that symptoms had been present for more than six months at the time of diagnosis in over 70 per cent of the patients. In 41 per cent symptoms had been present for more than a year and in 23 per cent the symptoms exceeded two years in duration. Furthermore, those patients whose symptoms were of less than six months' duration included those who never had symptoms at all as well as

those who received the benefit of early excisional surgery. The known duration of the disease has been extremely long in a number of cases. Instances have been reported where the known duration was at least seven or eight years, and in other cases the probable duration was as great as eleven to fifteen years. The statement sometimes made that it is typically a rapidly progressive fatal disease is therefore in error. Although rapid progression occurs in some cases, an indolent and protracted course is seen more often.

Physical Signs. The findings on physical examination are not helpful in the diagnosis of this disease. In early cases examination of the chest usually reveals no abnormal signs. When the process is more advanced, the findings will depend upon the extent and distribution of the disease and the presence or absence of secondary infection. In the presence of complications, such as pneumonia or suppurative pulmonary disease, the findings attributable to the complicating condition will overshadow those due to the neoplasm itself. The non-specific nature of the symptomatology and physical findings in patients with this tumor is emphasized by noting the original clinical impression in patients subsequently proved to have bronchiolar carcinoma. They have been diagnosed most frequently as pulmonary tuberculosis, but the working diagnosis has often been sarcoidosis, silicosis, bronchopneumonia, metastatic carcinoma, fungus disease, bronchiectasis, Hodgkin's disease or atypical pneumonia.

Radiographic Features. It has often been said that bilateral nodular lesions, varying in size from a millet seed to a cherry, rounded in contour but with indistinct margins fading imperceptibly into the surrounding lung and involving all lobes of both lungs, are characteristic of this variety of lung cancer. Fortunately, this is the *late* rather than the *typical* picture of this disease. While this picture is often seen in widespread, far advanced cases, it was encountered in but 20 per cent of a large series of patients at the time of the first chest x-ray which demonstrated their lesion. As a matter of fact, the most frequently encountered radiographic picture at the time of the patient's first chest x-ray was that of a solitary peripheral nodule, usually of small size. This was the initial x-ray finding in 26 per cent of the reported cases. In reality there is no roentgenographic picture that is characteristic of bronchiolar carcinoma and it may mimic any type of pulmonary disorder. It has been customary in the past to divide these lesions into two types: the diffuse[8] and the nodular.[9] This is a purely artificial distinction, for these merely represent different stages of the same process. With continued growth, the discrete nodules tend to coalesce to form solid masses. Furthermore, the growth characteristics and manner of extension of this tumor vary in different portions of the lungs of the same patient. One patient may show discrete nodules in one lobe or lung and diffuse consolidation in another lobe or the opposite lung. It is more common to find lesions of both types in a single patient than to encounter a patient in whom the lesions are exclusively nodular or one with diffuse consolidation alone. More than two-thirds of the patients show unilateral lesions on their first chest roentgenograms, and in about one-half of the cases the tumor is confined to a single lobe at the time of the original demonstration of the disease. Postmortem examination in the fatal cases, however, shows extensive bilateral lesions much more frequently.

Methods of Diagnosis. This disease was first described by Malassez[9] in 1876, but the diagnosis was not made in a living patient until 1936 when Skorpil[10] performed a left upper lobectomy for a lesion which proved to be a bronchiolar carcinoma. It is not surprising, then, to find that postmortem examination has been the most frequent method of diagnosis of this neoplasm. Wood and Pierson[11] performed a lobectomy in February, 1943, for a pulmonary lesion of uncertain etiology which proved to be a bronchiolar carcinoma, and since that time seventy-five patients of record have been correctly diagnosed during life.[2] Two developments account for the fact that in recent years it has been possible to diagnose this lesion at a time when it may still be amenable to treatment. First among these is the aggressive use of early excisional surgery in the management of patients with solitary peripheral nodules or persistent pulmonary infiltrates of uncertain etiology. A second and most promising diagnostic method is the use of the Papanicolaou exfoliative cytologic technic in the examination of the sputum of patients suspected of having bronchiolar carcinoma. Papanicolaou has noted that this tumor exfoliates profusely and yields abundant material characteristic of this type

of neoplasm.[12] Good and associates,[13] and McDonald and Woolner[14] also believe that in certain instances cells in the sputum possess characteristics that will permit the examiner to suggest the diagnosis of bronchiolar carcinoma. The typical findings consist of clumps of columnar cells with a free border of cytoplasm and fairly regular nuclei. It is probable that these clumps represent groups of cells which formed papillar projections within the alveoli which have broken off and been expectorated. The value of the Papanicolaou technic is strongly suggested by the report of Watson and Smith[15] from the Memorial Hospital in New York City. Among a group of fifteen patients proved to have bronchiolar carcinoma, the sputum was either positive or strongly suspicious of cancer in 80 per cent. Other diagnostic methods include needle biopsy, lung biopsy at open thoracotomy and peripheral lymph node biopsy in patients with metastatic disease. These latter methods are usually of value only in the patients with extensive and widespread disease when the diagnosis is of considerable interest but little practical importance.

Metastases. Metastatic lesions are present in approximately 50 per cent of patients with bronchiolar carcinoma.[2,16] A thorough review of all reported patients with this cancer provides strong support for the opinion of Watson and Smith[15] that metastases are most frequent to the same lung, the opposite lung or the hilar nodes. Distant spread occurs most commonly to the liver, abdominal nodes, bones, adrenals, brain, kidneys, cervical nodes, spleen and heart in that order of frequency. Among the patients with metastases, approximately one-third of them will show local spread only. Another one-third of this group will show both local and distant spread, while the remaining third will show distant spread only. Thus roughly two-thirds of the patients with metastatic disease will show involvement of the intrathoracic lymph nodes. The fact that almost one-third of the patients with metastatic disease show distant spread only demonstrates the frequency of blood-borne metastases. There is convincing evidence to indicate that metastases may take place by either of the following four routes: (1) local invasion, (2) lymphatic spread, (3) blood-borne metastases and (4) bronchogenic dissemination. Proof that these tumors spread by local extension, by the lymphatics and by the blood stream is conclusive and unmistakable. The concept of aerial metastases or bronchogenic dissemination is one having important therapeutic implications. There are many competent observers who believe that this tumor is of multicentric origin, but this theory has never been proved. On the contrary, much data have been accumulated to support the belief that they arise unicentrically and spread by the air passages as well as by more conventional routes.[2,17] The concept of bronchogenic spread of this tumor is strongly supported by the established ease with which the tumor cells and papillary tumor projections desquamate, by the findings of these cells in distant bronchi and by the relative frequency with which exfoliative cytologic studies yield positive findings. Metastases to other lobes of the same lung and to the opposite lung by way of the blood stream, the lymphatics and the bronchial tree strongly support the unicentric as opposed to the multicentric origin of this tumor. Numerous cases may be cited to prove that it is frequently of long duration and that it often behaves in an indolent manner.[2,18,30] The late appearance of apparently new lesions following resection may therefore reasonably be considered as metastases which were present but not evident at the time of surgery rather than as an example of multicentric origin.

Treatment. Excisional surgery is the only hopeful form of treatment for this neoplasm. It does not respond to irradiation nor is it favorably affected by cytotoxic agents. The peculiar growth characteristics and manner of spread of bronchiolar carcinoma suggest that conservative pulmonary resection is the treatment of choice in the majority of patients. When the distribution of the disease makes such a procedure feasible, the involved lobe or lobes should be removed unless there is proved or strongly suspected involvement of the mediastinal lymph nodes. In that situation a total pneumonectomy and radical mediastinal lymph node dissection should be performed. Otherwise, pneumonectomy should be reserved for those patients in whom the distribution of the disease makes that operation mandatory. The justification for conservative pulmonary resection in the treatment of this tumor lies in the fact that approximately 50 per cent of the patients will show no metastases at the time of their death. Of the total group, approxi-

mately 20 per cent demonstrate both local and distant spread, while about 15 per cent will show distant spread only.[2] Therefore, about 85 per cent of all patients with this tumor could not be permanently benefited by radical pneumonectomy as customarily employed in the treatment of bronchogenic carcinoma. The remaining 15 per cent, who will show only mediastinal lymph node involvement, may or may not be cured by such an operation. One must balance this potential benefit against the likelihood of an undetected spread to the opposite lung, requiring excisional surgery on that side at some future time if previous contralateral pneumonectomy has not made such an operation unfeasible.

Prognosis. Excisional surgery has been employed in the treatment of this neoplasm for too short a time to permit definite conclusions to be drawn as to results. Among a group of fifty-seven reported patients treated by resection whose reports we have reviewed,[2] thirty-seven were alive from six months to more than five years postoperatively. Twenty-six of the thirty-seven survivors were free of disease at the time of their last follow-up examination. Five of these patients had been operated upon more than five years previously. Among five personal patients with this tumor, one had extensive bilateral disease and died without definitive surgery. A second patient had a recurrence five months after his original operation and a second resection was performed; however, he again has recurrent disease which will almost surely prove fatal. The remaining three patients are alive and well, one more than five years postoperatively, the second more than three years postoperatively and the third approximately one year after operation.

SUMMARY AND CONCLUSIONS

1. The pulmonary neoplasm which has been referred to as bronchiolar carcinoma, alveolar cell carcinoma, alveolar cell tumor, pulmonary adenomatosis and by numerous other similar or related titles represents a single entity which varies only in its degree of malignancy in different patients or in different portions of the same lesion.

2. The site of origin of this tumor has not been clearly established but the preponderance of present day opinion inclines to the belief that it arises in the terminal bronchioles, and histologic studies appear to bear this out. The important clinical fact that it arises peripherally has been shown conclusively.

3. Although there are many who believe this lesion to be of multicentric origin, convincing proof of this theory has never been offered. On the contrary, there is much evidence to suggest that it arises unicentrically and spreads to other parts of the lungs and to distant sites by direct invasion, the lymphatics, the blood stream or by bronchogenic dissemination. Slightly over 50 per cent of patients show metastatic lesions at autopsy. It has been shown repeatedly that this tumor may behave in an indolent manner. The late appearance of new lesions in the same or the opposite lung after resection of the primary growth can be more logically explained on the basis of an undisclosed preoperative spread than by the unproved theory of multicentric origin.

4. Unfortunately there are no clinical features or roentgenographic characteristics whereby these tumors can be definitely recognized. The symptoms are those of any chronic pulmonary disease and the physical findings depend upon the location, character, extent and distribution of the disease. The radiographic picture may mimic that of virtually any type of pulmonary disorder.

5. It has been stated frequently that bronchiolar carcinoma or pulmonary adenomatosis is characterized by diffuse nodular lesions involving all lobes of both lungs and by the expectoration of huge quantities of glairy mucoid sputum. While this is a fair description of certain patients with this disease, it is not typical of the average patient nor is it presented by those patients in whom an accurate diagnosis is therapeutically important.

6. Two diagnostic methods have proved helpful in the study of patients with this tumor. The most important of these is histologic examination of the resected specimen from patients who present with solitary peripheral pulmonary nodules or persistent pulmonary infiltrates of uncertain etiology. A second valuable aid in these patients is cytologic examination of the sputum or bronchial aspirate by the Papanicolaou method. Exfoliative cytologic studies have shown a high degree of accuracy in the diagnosis of this tumor.

7. The treatment of choice of bronchiolar

carcinoma is conservative excisional surgery. This implies lobectomy when such an operation is feasible. If there is multiple unilateral lobar involvement or demonstrable mediastinal lymph node metastases, total pneumonectomy and radical mediastinal node dissection become mandatory.

8. Surgical treatment of this condition was begun too recently to permit conclusive statements to be made concerning prognosis. Evidence is accumulating, however, to suggest that with early excisional surgery the prognosis in patients with this tumor may be appreciably better than in those with bronchogenic carcinoma.

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Treatment of the Inoperable Pulmonary Cancer, Primary and Metastatic*

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THERE are an estimated 20,000 new cases of primary bronchogenic carcinoma diagnosed each year in the United States, and the number seems to be increasing. Probably less than 5 per cent of these cases are satisfactorily controlled by surgery. In addition, the lung is a common site for metastatic cancer, and the mediastinum for lymphomatous diseases. The estimated frequency with which pulmonary metastases occur in various types of cancer is shown in Table 1. About 25 per cent of all patients dying of cancer have pulmonary metastases, but data on the proportion with respiratory symptoms are lacking. It is apparent that some patients with pulmonary metastases have no symptoms. In others the disease is so generalized that the pulmonary disturbances are only a minor part of the total picture, while in a third group respiratory symptoms constitute the major problem. This last group comprises approximately one-third of the patients with lung metastases, or about 20,000 new patients each year in the United States.

The most effective method of treatment is to interfere with the growth and extension of the neoplastic cells. This can be accomplished to a limited degree with ionizing radiation or specific drugs. The presentation of the methods of application of these agents and the indications for their use is the primary purpose of this report. A number of non-specific measures which may alleviate some of the manifestations and secondary complications of the growing tumor will also be mentioned. The objectives of treatment are the relief of discomfort, improvement in function and restoration of the patient to a tolerable and possibly useful activity for as long as possible.

PRINCIPLES OF GENERAL MANAGEMENT

The following remarks are based on the assumption that the lesion has been first carefully evaluated from a surgical point of view.

TABLE 1
APPROXIMATION OF THE INCIDENCE OF PULMONARY METASTASES AT AUTOPSY

Primary Site of Cancer	Estimated No. of Deaths in U. S. per Year	Pulmonary Metatases (%)
Breast	25,000	
Kidney	4,000	
Bone	2,500	50–70
Thyroid	1,000	
Testes	1,000	
Pancreas	8,000	
Ovary	6,000	25
Adrenal	600	
Intestine	35,000	
Uterus, including cervix	18,000	
Prostate	12,000	20
Liver	8,000	
Esophagus	4,000	
Stomach	25,000	
Bladder	7,000	15
Head and neck	6,000	
Lymphomas and leukemia	15,000	50–90

Accurate Diagnosis. The presence of cancer, its type and extent must be clearly established. The presence of primary cancer elsewhere in

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the body is not certain evidence that a pulmonary lesion is metastatic cancer; it may be an infectious process or a new primary neoplasm. The type of metastatic cancer is sometimes an important factor in determining therapy. Increase in pulmonary signs in the presence of a known pulmonary neoplasm is not necessarily due to extension of the disease, as illustrated by the following case:

CASE 1. Fever and chest pain developed in a thirty-three year old man. X-ray examination showed a mediastinal mass, and a diagnosis of Hodgkin's disease was established by biopsy at thoracotomy. Treatment consisted of triethylene melamine (TEM) and x-ray therapy to the mediastinum. The patient continued to lose weight, have intermittent fever and weakness, and persistent drainage of purulent material from the thoracotomy wound. Reexploration revealed an extrathoracic sinus tract. Because of this and the progression of symptoms the patient was treated on the presumption that his pulmonary problem was due to active Hodgkin's disease. He received local radiation to the sinus tract and TEM, with no improvement. Subsequently a diagnosis of empyema was made, and exploratory thoracotomy was performed. A large empyemic cavity was drained. Biopsy of the wall of the cavity did not reveal Hodgkin's disease. The patient improved rapidly, gained 20 pounds and returned to his full activity. At present, a year and a half after the drainage of the empyema, there is no evidence of recurrent Hodgkin's disease.

Evaluation of Pulmonary Disturbances. Infiltrating cancer makes little distinction between the pulmonary parenchyma, the great vessels, the mediastinum, the heart and chest wall. Different types of pulmonary lesions result in a wide variety of symptoms, so that an accurate understanding of the anatomic and physiologic disturbances is desirable before instituting therapy.

Anatomic disturbances: The various sites of tumor involvement are shown diagrammatically in Figures 1 and 2. The principal mechanism whereby complications are produced are those of mechanical obstruction and direct extension. An occluding endobronchial tumor characteristically leads to atelectasis or obstructive emphysema. Pneumonitis, bronchiectasis and abscess formation are the infectious sequellae of such lesions. Occasionally the obstruction may be perivascular or endovascular with resultant pulmonary hypertension. Parenchymal lesions may be "silent" or, when extension to the pleural surface occurs, may produce such complications as pleural effusions, pneumothorax or bronchopleural fistula. Great vessel

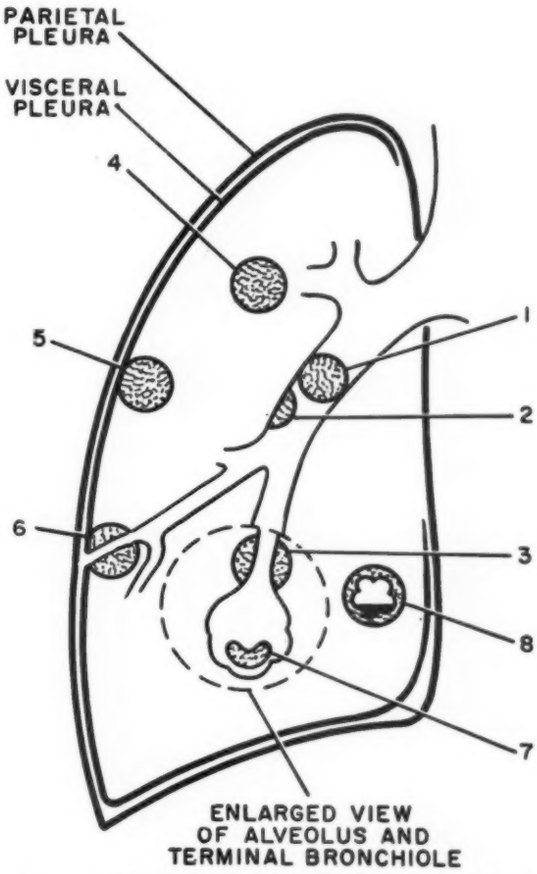

FIG. 1. Diagram showing involvement of lung structures, *per se*, with cancer. (1) Intrabronchial tumor occluding bronchus causing atelectasis (with or without shift of the mediastinum). (2) Lesion causing partial obstruction leading to obstructive emphysema, unilateral wheezing ("asthma") or mucosal ulceration with bleeding (hemoptysis). The infectious sequellae of such a lesion include obstructive pneumonitis, distal bronchiectasis, abscess formation or cavitation. (3) Peribronchiolar, endovascular or endolymphatic sites may cause pulmonary hypertension, cor pulmonale (dyspnea, heart failure). (4) Lesion involving parenchyma only. These may produce no symptoms. (5 and 6) Lesions involving the pleura causing pleurisy, with or without effusion (dyspnea, pain), pneumothorax or bronchopleural fistula. (7) Alveolar deposition of cancer or septal thickening due to malignant infiltration or fibrosis (dyspnea, anoxemia). (8) Lesion with central necrosis and cavitation (confusion with tuberculosis). Redrawn and modified after CHURCHILL, E. D., in Christopher's Textbook of Surgery.

obstruction with the production of the superior vena caval syndrome is often encountered, as is recurrent laryngeal nerve paralysis. Many other clinical problems resulting from specific anatomic disturbances produced by the cancer are described in Figures 1 and 2.

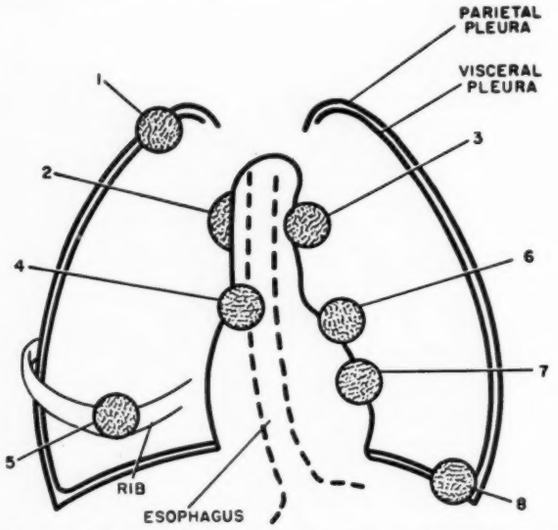

FIG. 2. Diagram showing involvement of contiguous structures of the lung by cancer. (1) Superior sulcus tumor with involvement of the brachial plexus causing shoulder, arm and hand pain; sympathetic nerve involvement (Horner's syndrome). (2) Invasion and compression of great vessels giving rise to the superior vena caval syndrome. (3) Lesion which may compress recurrent laryngeal nerve (vocal cord paralysis and hoarseness) or phrenic nerve (diaphragmatic paralysis). (4) Tumor within hilar nodes (cough); occasional invasion of esophagus causing obstruction (dysphagia) and ulceration (hematemesis). (5) Tumor which has invaded rib and chest wall causing pathologic fracture, pain. (6) Lesion which has invaded pericardium causing pericarditis with or without effusion (pain, possible tamponade). (7) Invasion of the myocardium by tumor leading to arrhythmias and cardiac failure. (8) Tumor invading the diaphragm. Redrawn and modified after CHURCHILL, E. D., in Christopher's Textbook of Surgery.

Physiologic disturbances: The anatomic disturbances just considered may ultimately lead to marked physiologic derangements. Figure 3 illustrates diagrammatically a basic pulmonary unit: an alveolus with its associated capillary and respiratory bronchiole. The unit is subject to the negative pressure in the pleural space. If the various anatomic sites of malignant disease (Figs. 1 and 2) are related to this diagram, the way in which physiologic disturbances are produced may be understood. For example, peribronchiolar or endobronchial obstruction will impair CO_2 elimination by the lungs in the segment or lobe involved. Depending upon how many vascularized pulmonary units are involved, this may result in an elevated CO_2 content in the patient's blood and respiratory acidosis. We have observed a patient with diffuse pulmonary reticulum cell

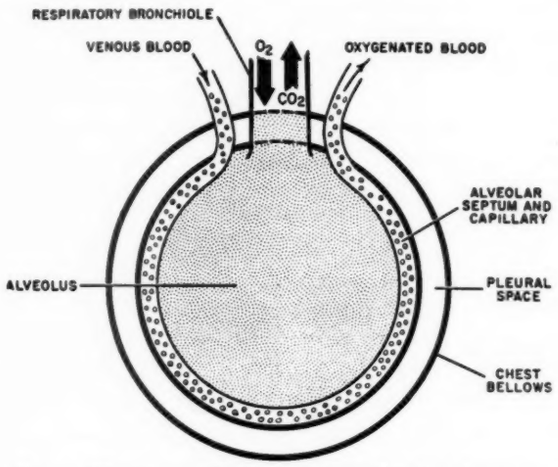

FIG. 3. Diagrammatic illustration of basic pulmonary unit. The alveolus is pictured as a large air sac surrounded by a septum containing a capillary. Respiratory gases enter and leave through the respiratory bronchiole. This functioning unit is pictured as being subject to the negative pressures induced in the pleural space by the action of the chest bellows (intercostals, diaphragm, accessory muscles of respiration).

sarcoma in whom respiratory acidosis developed on this basis. Following the administration of nitrogen mustard, shrinkage of the tumor occurred and the respiratory acidosis was corrected.

As another example, the effect of a large pleural effusion or massive tumor invasion of the pleura can be considered. Functioning units would be collapsed because of the extrinsic pressure, and the effectiveness of the chest bellows in inducing negative pressures would be limited. Inadequate ventilation of the alveoli would result, leading to dyspnea and possibly CO_2 retention.

Carcinomatous endarteritis may be visualized in the diagram as obstructing the pulmonary blood flow. When there is extensive obstruction, pulmonary hypertension and cor pulmonale may result.[11] Thickening of the alveolar septa and interstitial fibrosis may lead to impairment of gaseous exchange across the capillary membrane. Studies have been reported[1] on patients with such lesions due to lymphangitic spread of cancer. The physio-

logic disturbance encountered was alveolo-respiratory insufficiency with anoxemia.

It is admittedly difficult to analyze thoroughly the anatomic and physiologic aspects behind the symptomatology which each patient presents. However, the approach previously suggested will often help to clarify the situation. Treatment, both specific and supportive, can be more effectively administered if directed at the underlying disturbance.

TREATMENT

In general, active therapy is indicated in the management of inoperable cancer, particularly when definite symptoms are present.[7] Specific and supportive measures are discussed separately.

Specific Therapy. This refers to agents given for the purpose of destroying the cancer or inhibiting its growth. The application of specific therapy will be discussed for the different forms of cancer.

Primary bronchogenic carcinoma: The natural progression of inoperable or recurrent bronchogenic carcinoma is usually rapid, and approximately 70 per cent of the patients die within one year after the clinical onset of the disease.

If at thoracotomy the primary tumor or metastatic lymph nodes are not resectable, they should be implanted systematically with radon seeds. Radon seed implants deliver a high tumor dose of 8,000 to 12,000 r with minimum risk of radiation damage to surrounding structures. It is also a useful method for marking the anatomic limits of the tumor and involved lymph nodes for a subsequent course of x-ray therapy. In inoperable cases without evidence of distant metastases radiation therapy is advisable even in the absence of disabling symptoms, because as the disease spreads such symptoms are likely to appear within a short time. In the presence of symptoms, whether distant metastases are already evident or not, x-ray therapy produces relief of bronchial obstruction, cough, dyspnea and hemoptysis, or of mediastinal pressure symptoms in about 70 per cent of the patients.

Bronchogenic cancer is best irradiated with supervoltage x-rays (1,000 to 2,000 kv.) or with hard gamma rays (telecobalt). For epidermoid and differentiated adenocarcinoma a tumor dose of 6,000 r in five to six weeks is given when there is a chance for prolonged control of the disease. A smaller dose is indicated if the intrathoracic metastases are more extensive. In anaplastic (oat-cell) carcinoma the high probability of hepatic and cranial metastases reduces the possible survival time to a few months. Therefore, we prefer, for the convenience of the patient, to shorten the period of treatment to the primary lesion, and a 3,000 r tumor dose is given in nine days.

Palliation has been most successful when the disease was largely confined to the mediastinum or a single portion of the lung. It is less effective in widespread disease, with involvement of the parenchyma of both lungs, such as occurs in terminal bronchiolar carcinoma. Nevertheless x-ray therapy may be of benefit. The more heavily involved lung is irradiated first with a tumor dose of 2,000 r in eight days; if there is a satisfactory response, the other lung is similarly treated.

Large tissue doses in excess of 2,500 r will cause some degree of pneumonitis beginning two to eight weeks after irradiation. Radiation pneumonitis sometimes resolves completely or partially, sometimes progresses to pulmonary fibrosis and sometimes cannot be differentiated from lymphatic spread of carcinoma. Radiation pneumonitis may be alleviated in some cases by cortisone, 200 to 300 mg./day, and antibiotics should always be used to prevent secondary infections.

In some instances of far-advanced disease nitrogen mustard (HN2)* is used in conjunction with x-rays.[5] Provided the hematologic status of the patient is within normal limits, a single dose of 0.4 mg./kg. (20 to 30 mg.) in the average adult is given intravenously, usually into the tubing of an infusion. This dose will induce several hours of nausea and vomiting, beginning within one-half to two hours. Sedation with sodium amytal or chlorpromazine may diminish the vomiting. On the basis of observations in the laboratory we have given a course of HN2 immediately preceding the onset of x-ray therapy in order to produce additional injury to the tumor cells. While the value of this combination has not been established clinically, it seems reasonable to continue its use in patients with large tumors. There is a more definite reason for using HN2 in patients presenting with symptoms due to compression of the superior vena cava. These patients are uncomfortable with edema and

* Mustargen® (Merck & Co., Inc., Rahway, New Jersey).

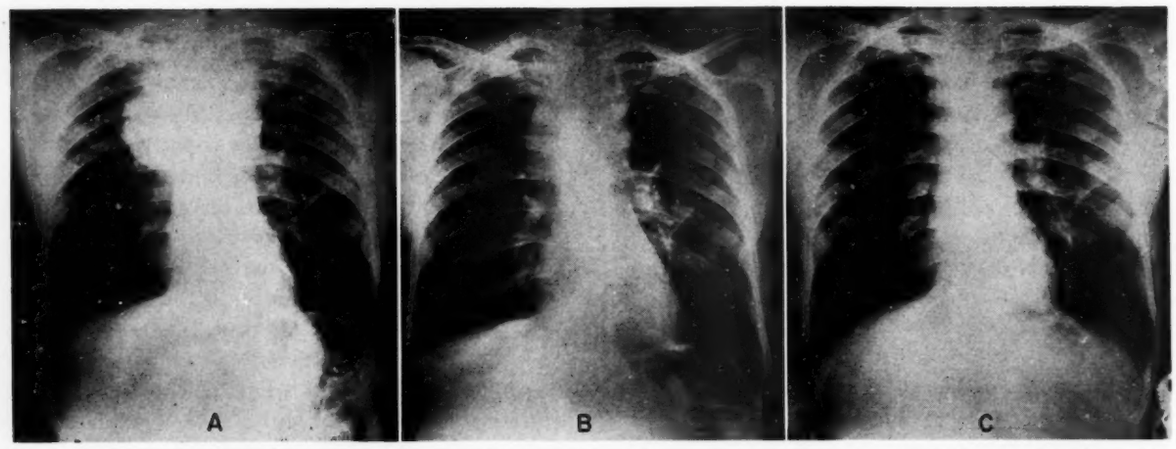

FIG. 4. Case 11. A forty-four year old man with bronchogenic oat-cell carcinoma was admitted with signs of a superior vena caval syndrome. A, film taken January 21, 1952, showed a middle superior mediastinal mass. The patient received 6 mg. of TEM intravenously on January 20th and January 21st; and since he was not improved, on January 23rd he received 0.3 mg./kg. HN2. There was prompt symptomatic relief. B, film taken January 30, 1952, showed regression of mediastinal mass. A tumor dose of 3,000 r was given to the mediastinum. C, film taken February 13, 1952, showed further improvement. The patient had a ten-month remission. Manifestations of the disease due to generalized metastases occurred in November, 1952, and the patient died April 2, 1953, with evidence of severe liver insufficiency due to metastatic disease.

venous engorgement of the face, neck and arms, increased venous pressure, and dyspnea and orthopnea. HN2, usually given as 0.4 mg./kg. in a single dose, will produce prompt relief of this syndrome in 80 to 90 per cent of the patients, with objective evidence of tumor regression. Improvement is due in part to a reduction of the inflammatory reaction and edema in the mediastinal and cervical nodes, but histologic changes have been observed in the tumor cells similar to those following x-ray therapy.[3] The treatment is given in a single injection so that if effective, it will result promptly in improvement. Usually, patients with anaplastic or oat-cell carcinoma show the most striking response. If the response is incomplete and the patient's blood count is not unduly depressed in three weeks, another dose of 0.2 or 0.4 mg./kg. of HN2 may be given. The serious reaction of edema in the tumor bed and lymph nodes, such as sometimes occurs after the initiation of x-ray therapy, has not followed the use of HN2. The remissions induced by HN2 are brief, lasting three to eight weeks, and second courses of treatment are usually not as effective.[5] Therefore, it is desirable in most cases to start x-ray therapy within one week. Figure 4, Case 11, describes a patient treated in this manner.

Recurrent pleural effusion in lung cancer may be due to mediastinal, parenchymal or pleural disease. When evidence of pleural involvement exists, x-ray therapy, the intrapleural instillation of radioactive gold (Au^{198})[6] or HN2 may control the effusion.[5] The usual procedure is to remove most of the pleural fluid and instill Au^{198} or HN2 into an almost dry pleura. The usual dose of Au^{198} is 75 to 100 mc. and of HN2, 20 to 30 mg. One of these treatments will be effective in most instances in relieving the need for frequent thoracenteses. Occasionally triethylene melamine (TEM), an oral drug with nitrogen mustard-like activity, has been used in widespread lung cancer. The usual dose is 5 to 10 mg. the first week taken one hour before breakfast with plain water, and further dosage is determined at weekly intervals on the basis of the peripheral blood picture.[4] Although the effects of TEM are similar to those of HN2, the latter is preferred for promptness and consistency of action. While treatment may control the pulmonary disease, lung cancer disseminates widely and the disturbances produced by distant metastases often overshadow the local problems.

Metastatic cancer to the lungs: With the exception of carcinomas of the breast, prostate and thyroid, and the lymphomas and leukemias, which may be treated by special methods, carcinomas and sarcomas metastatic to the lungs are managed according to the principles outlined for lung cancer. It is recognized even more conspicuously in these tumors that some

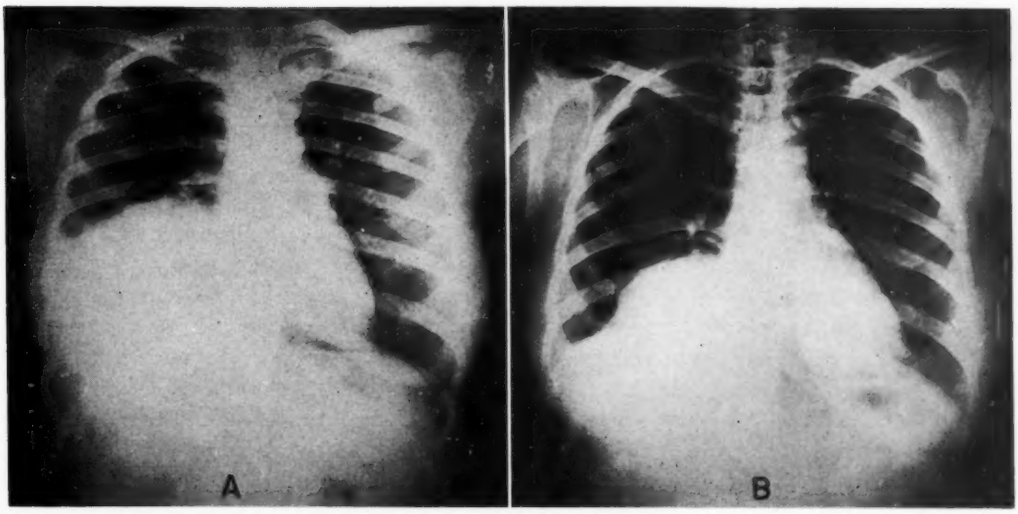

FIG. 5. Case III. This twenty-eight year old woman was given the diagnosis of chorioepithelioma in November, 1947, following the birth of her second child. A panhysterectomy and bilateral salpingo-oophorectomy were performed at that time. The patient re-entered the hospital in May, 1948, complaining of severe dyspnea, fever and pain. A, pretreatment film taken June 7, 1948, showed a large mass in the right lower lung field. The patient was given 11 mg. of HN2 intrapleurally on June 17th and 11 mg. of HN2 intravenously the next day. B, film taken November 2, 1948, showed decrease in size of mass and resorption of fluid. There was a six-month remission with decrease in size of chest mass, resorption of pleural effusion, 35 pound weight gain and complete relief from chest pain, dyspnea and fever. In December, 1948, symptoms recurred and x-rays revealed metastases in both lung fields and pleural effusion on the right. The patient was given 12 mg. of HN2 intravenously on January 25 and January 28, 1949, and 10 mg. of HN2 intrapleurally the next day. Brief symptomatic improvement occurred but there was no change in the chest film. The disease progressed and the patient died on March 20, 1949.

may increase in size slowly and produce virtually no symptoms.

Pulmonary metastases are, in general, no less responsive to irradiation than metastases elsewhere, but radiation pneumonitis and fibrosis are limiting factors in the treatment.

A solitary pulmonary metastasis of whatever origin may be resected if there is no evidence of disease elsewhere.

Multiple pulmonary metastases of seminoma, chorioepithelioma, lymphosarcoma, neuroblastoma and other radiosensitive cancers may be irradiated even in the absence of symptoms, since a tumor dose of 2,000 to 2,500 r to the whole chest can cause their disappearance without producing more than temporary pneumonitis. Five-year radiation survivals are recorded in patients with pulmonary metastases from seminoma, chorioepithelioma, Ewing's and Wilms' tumors, and recticulum cell sarcomas. Apart from the preceding, irradiation of multiple pulmonary metastases is not usually advisable except for the relief of symptoms. Hemoptysis is sometimes a problem and can usually be stopped by a tumor dose of 2,000 r; if the site of hemoptysis cannot be determined, it is our practice to irradiate the largest metastasis first. Chronic cough and excessive sputum may be alleviated, although the relief is often of short duration. We prefer to irradiate the more involved lung first (tumor dose 2,000 to 2,500 r), and to avoid irradiating the remaining lung for as long as possible. Dyspnea may also be improved, but less frequently than cough or sputum.

X-ray therapy is sometimes preceded by a course of HN2 or TEM; also these drugs used alone may cause a favorable response. (Fig. 5, Case III.)

Breast cancer: Pulmonary metastases occasionally respond to hormonal control measures; a number of technics are available for altering the hormonal balance and the indications for each method are being more clearly defined by experience.[8,9]

In premenopausal patients with inoperable or recurrent disease the usual sequence of therapy is as follows:

Surgical castration is preferred (radiation castration may be effective). After evaluating the response, if no improvement occurs or if improvement is followed by relapse, androgen therapy is started, usually 100 mg. of testoste-

rone propionate injected intramuscularly three times weekly. If there is a favorable response, when the patient relapses on therapy, further improvement may follow its discontinuation.

Adrenalectomy has caused further improvement, particularly in situations when the patient has been benefited by castration and testosterone. In some clinics adrenalectomy is the first procedure used in patients who have relapsed following a response to castration.

Hypophysectomy has not been adequately evaluated in patients refractory to other hormonal control measures, but regression of pulmonary metastases has been seen following hypophysectomy.

Cortisone, 200 to 300 mg./day, may produce temporary improvement in patients resistant to castration and testosterone.

These methods should be applied in an orderly sequence so that the effect of one procedure is evaluated before initiating another.

In postmenopausal women hormonal control measures have consisted, usually in a sequence which varies in different clinics, of trials of estrogens, androgens, castration (radiation or surgical), combined adrenalectomy and castration, and of cortisone in far advanced cases. Some degree of objective response occurs in about 50 per cent of the cases with widespread breast cancer.

Besides the established value of these methods, x-ray therapy has been effective in temporarily relieving pulmonary symptoms. Treatment is directed to the local manifestations of disease in the mediastinum and pulmonary parenchyma. Also, recurrent pleural effusions have been effectively controlled by x-ray therapy. Recently intrapleural Au^{198} has been used for the same purpose.

In some instances the polyfunctional alkylating agents, such as nitrogen mustard, TEM, triethylene phosphoramide (TEPA) and triethylene thiophosphoramide (ThioTEPA), may have a favorable influence on pulmonary metastases. HN2 is usually given in a single dose of 0.4 mg./kg. intravenously, and TEM is given orally under careful dosage control as maintenance therapy.[4] Recurrent pleural effusions due to breast cancer may respond to the intrapleural injection of HN2 given in the manner described for lung cancer. Two patients illustrating favorable responses to HN2 and TEM, respectively, are shown in Figures 6 and 7, Cases IV and V.

Prostatic cancer: Pulmonary or osseous metastases from carcinoma of the prostate respond as remarkably to treatment as those elsewhere in the body. Either estrogen or surgical castration is effective in the majority of cases, and frequently a combination of estrogen and castration is used. Figure 8, Case VI, shows pulmonary metastases which responded to estrogen therapy.

Thyroid cancer: The natural course of thyroid cancer is varied, unpredictable and often protracted, even in patients with pulmonary metastases. The pulmonary lesions respond to x-ray therapy, and if they are capable of concentrating iodine, to radioactive iodine (I^{131}).[10] I^{131} in suitable patients is preferable. The potential response to I^{131} is well correlated with the histologic type; the alveolar and follicular tumors are more likely to pick up I^{131}. The patient is first given a tracer dose of I^{131} to determine how efficiently it is concentrated in the tumor. If selective uptake is demonstrated, the avidity of tumor cells for iodine may be further enhanced by removing the normal thyroid gland by surgery or destroying it by I^{131}. A further procedure is to administer thiouracil for six to eight weeks in order to block the uptake of iodine by the tumor. The tumor cells will show their maximum uptake of I^{131} two to three days after stopping thiouracil. The therapeutic dose of I^{131} is determined for each case on the basis of uptake of the tracer dose and estimated mass of tumor. The chief limiting factor in dosage is damage to the hematopoietic system; and the usual dose is in the range of 100 to 200 mc. by mouth. Figure 9, Case VII, illustrates a satisfactory response.

Lymphomas and leukemias: Early and apparently localized Hodgkin's disease of the mediastinum is usually treated vigorously by radiation therapy with a tumor dose in the range of 2,400 to 3,000 r in three to five weeks. If the disease is chiefly in the mediastinum but there is evidence of disease elsewhere, a smaller tumor dose in the range of 1,500 to 2,000 r is given. These doses are sufficient to produce prolonged and sometimes permanent disappearance of the local disease even though it recurs elsewhere. In an experimental series of patients with mediastinal and cervical or axillary disease we have given a course of HN2, 0.4 mg./kg., followed by 3,000 r tumor dose (1,000 kv.) to the tumor-bearing area. This

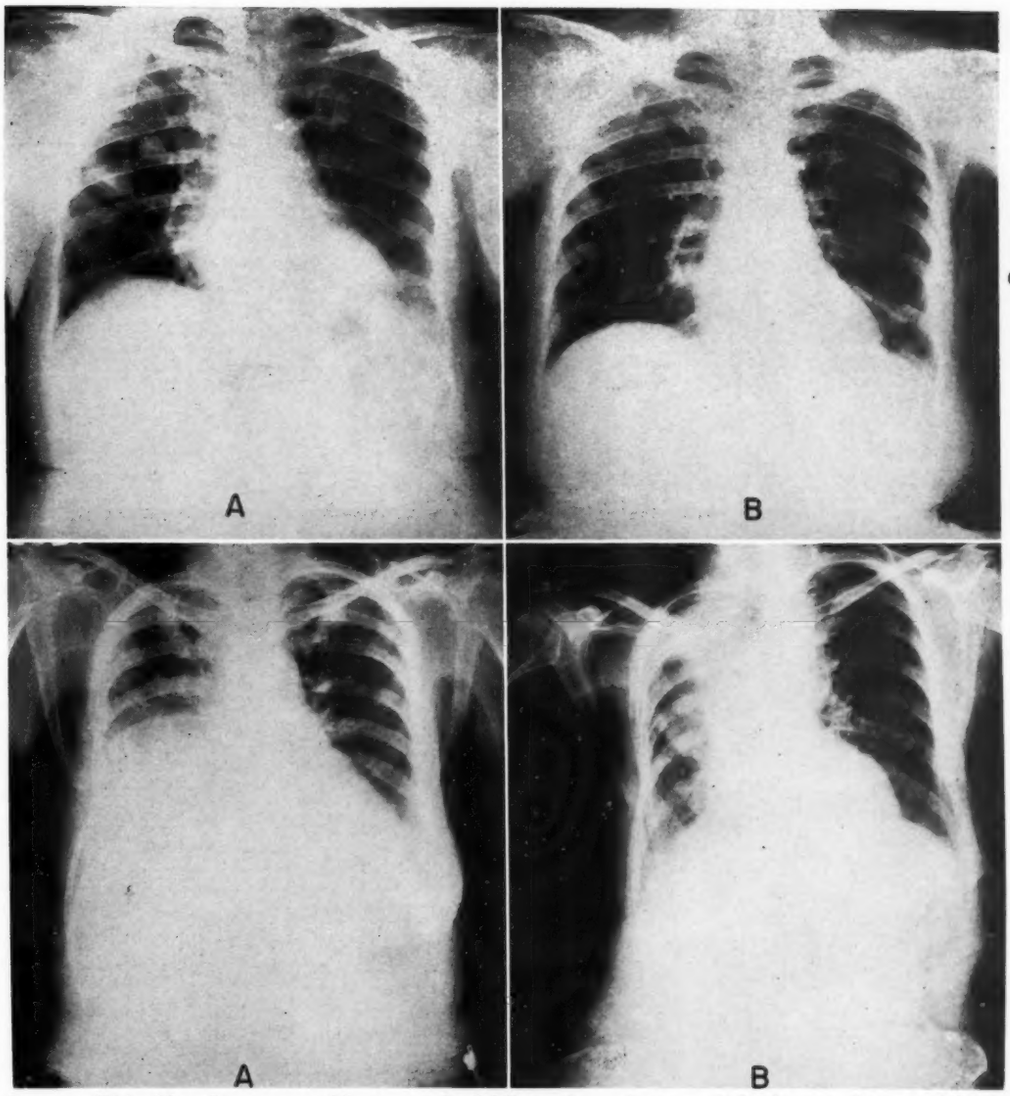

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FIG. 6. Case IV. This fifty-three year old woman had bilateral carcinoma of the breast diagnosed in July, 1952. Initial treatment was bilateral radical mastectomy. Pulmonary metastases were first noted in March, 1953. A, pre-treatment film taken July 2, 1953, showed metastatic nodules in upper portion of left lung field, mid-portion of right lung field and pleural reaction left base. The patient was started on oral TEM and received a total dose of 45 mg. between July 16 and December 3, 1953. There was rapid regression of pulmonary lesions. B, film taken March 2, 1954. Multiple osseous and hepatic metastases appeared at this time and the patient died on April 29, 1954.

FIG. 7. Case V. This fifty-four year old woman had carcinoma of the breast diagnosed in 1940 and was treated by right radical mastectomy. Pulmonary metastasis appeared in 1949, with progressive increase in pleural effusions, requiring thoracenteses monthly and then once or twice weekly. A trial of androgen and estrogen did not diminish fluid formation, and 2,000 r to the chest were without apparent benefit. A, chest film showed right pleural effusion on August 3, 1950. The patient received 0.4 mg./kg. HN2 intrapleurally. There was a rapid decrease in fluid formation, and marked symptomatic improvement. The disease, however, continued to progress slowly with osseous metastases, and the patient died on March 2, 1954.

treatment is well tolerated and it is given with the purpose of obliterating the disease. While it will take a number of years to demonstrate that this is a superior form of treatment, of five patients who were treated more than three years ago, thus far one has shown evidence of recurrent disease. A course of HN2 is also useful in treating bulky mediastinal and cervical disease. It will cause prompt regression of the enlarged nodes and then x-ray therapy can be given with less hazard and discomfort to the patient.

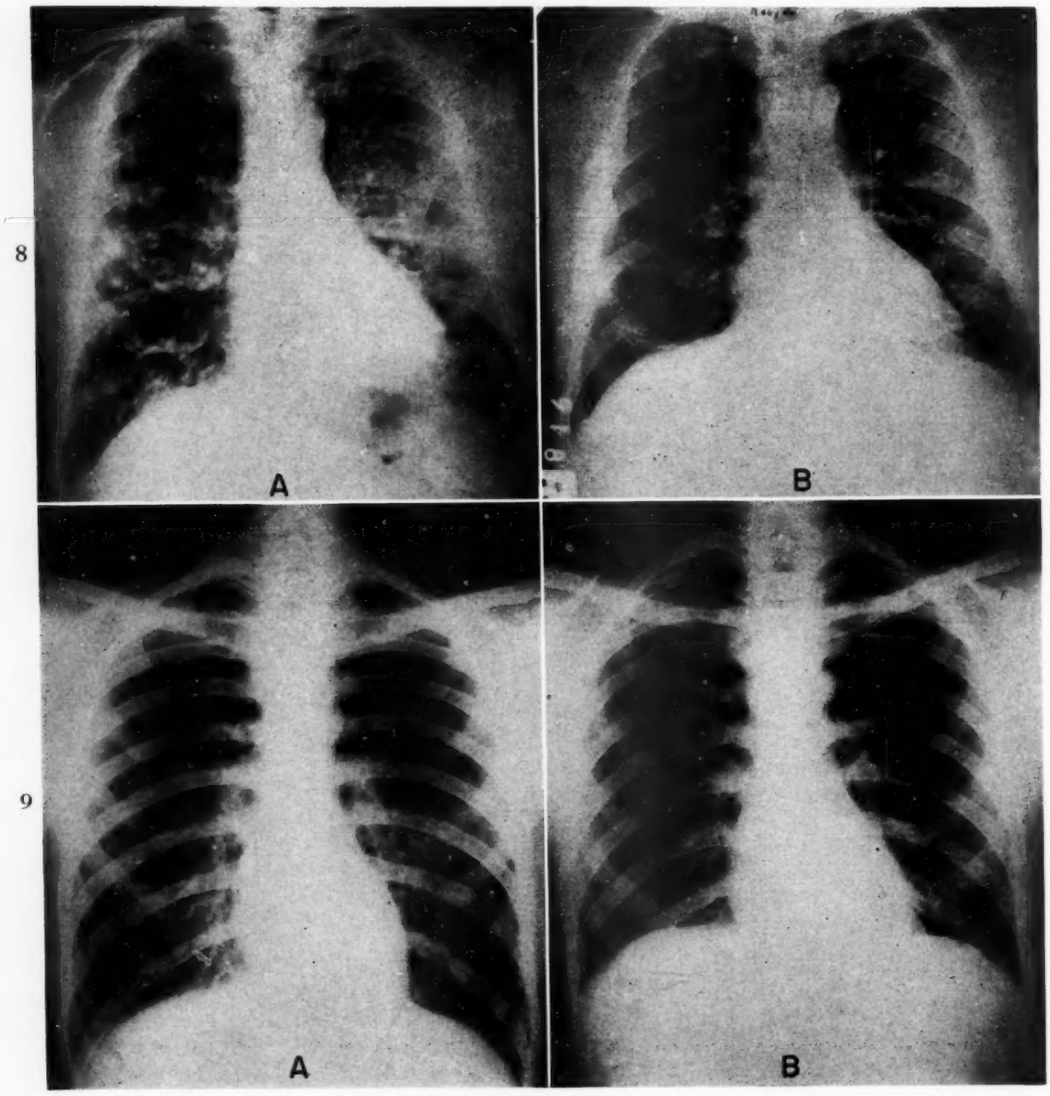

FIG. 8. Case VI. This seventy-one year old man had carcinoma of the prostate and pulmonary metastases diagnosed in August, 1949. A, pretreatment chest film. The patient was orchiectomized, and placed on 0.5 mg. estinyl estradiol daily. B, marked regression in the pulmonary metastasis in a film taken April 4, 1951, almost two years later.

FIG. 9. Case VII. This nineteen year old man had multiple pulmonary metastases from carcinoma of the thyroid, but no other evidence of disease. The diagnosis was made following thyroidectomy in September, 1948. A, pretreatment film taken April 23, 1949, showed multiple metastases of both bases. The patient received 133 mc. of I^{131} in July, 1949. B, film taken fourteen months later, September 21, 1950, showed decrease in pulmonary nodules. A second course of I^{131} was given in January, 1952, with further improvement. At present the patient is in good health and x-ray examination of the lungs reveals no evidence of disease.

For recurrent mediastinal involvement or parenchymal disease x-rays are the initial method of treatment. Radiation therapy should be given in doses adequate to cause tumor regression. In far advanced cases the pulmonary lesions may be the predominant problem, and they often show considerable resistance to x-rays. The dosage in these situations may be increased because the possibility of producing clinical improvement often overshadows the hazard of pulmonary fibrosis. In some of these instances, however, HN2 or TEM may be effective in relieving cough and dyspnea, and produce objective evidence of tumor regression. While the response to a course of HN2 usually lasts for only one to three months, TEM may be used as maintenance therapy. This type of response is shown in Figure 10, Case VIII. When pulmonary symptoms recur after x-ray, the response to a

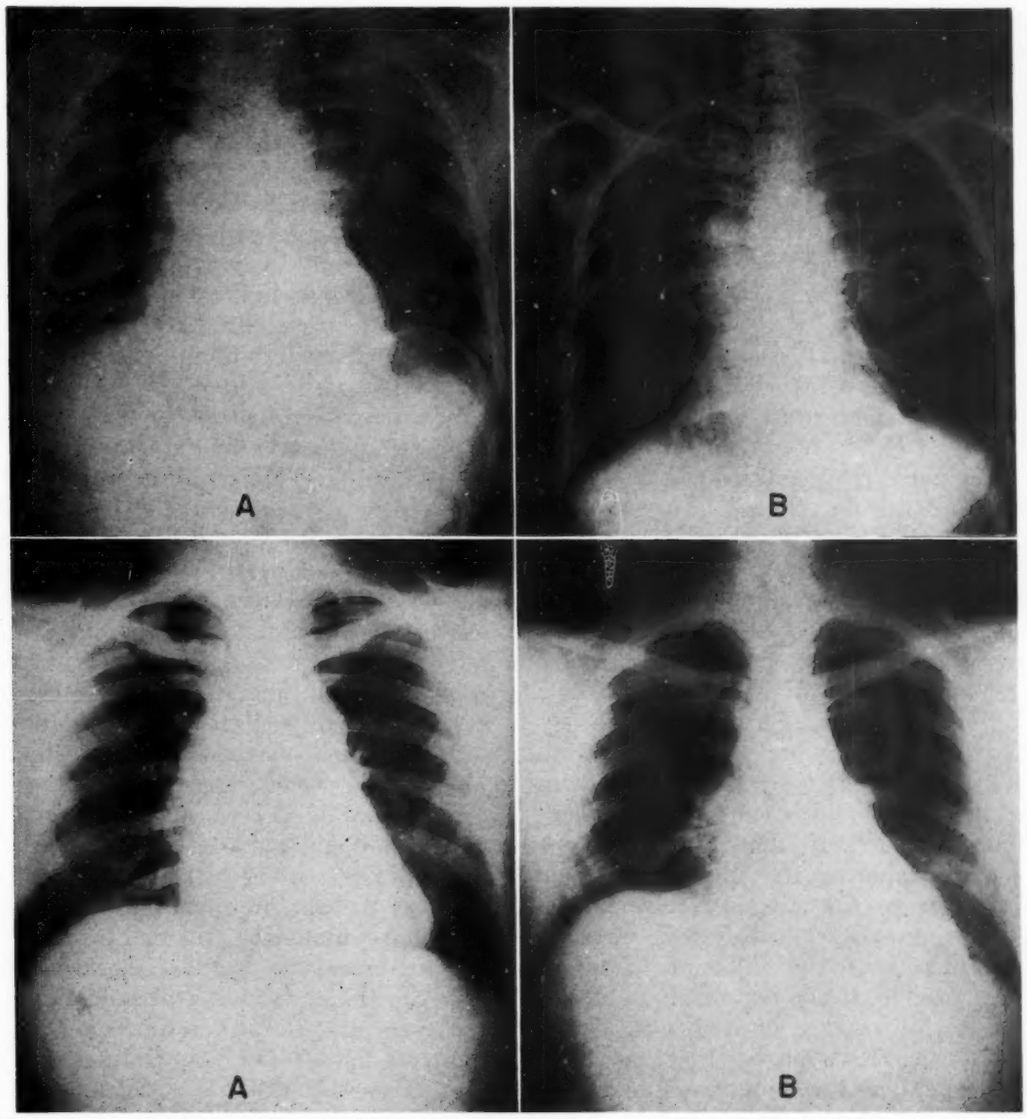

FIG. 10. Case VIII. This fifty-one year old woman had Hodgkin's disease diagnosed in August, 1946. The patient was treated with several courses of x-rays to enlarged cervical, axillary and mediastinal nodes. A, chest film taken in February, 1950, showed progression in mediastinal enlargement with pulmonary symptoms. The patient was placed on a maintenance dose of TEM, and showed marked symptomatic improvement with regression of the mediastinal widening. B, film taken September 5, 1951. Disease recurred elsewhere and the patient died October 23, 1951.

FIG. 11. Case IX. This thirty-three year old man had acute myeloblastic leukemia diagnosed in October, 1953. A, film taken October 23, 1953, showed mediastinal adenopathy. The patient received 6-mercaptopurine and obtained a complete hematologic remission. B, film taken February 23, 1954, showed regression of the mediastinal adenopathy. The patient had relapse in May, with increase in the mediastinal widening; and a second remission was induced with cortisone.

course of HN2 may be useful in deciding whether the symptoms are due to active disease or pulmonary fibrosis. Some patients with Hodgkin's disease finally go on to almost complete replacement of the lung by fibrotic tumor, which is refractory to therapeutic doses of x-rays or nitrogen mustard.

The varieties of lymphosarcoma are usually managed in the same manner as Hodgkin's disease, although they do not respond as consistently to treatment. Some forms of the disease may be extremely sensitive to therapy, and small doses of x-rays, 200 to 400 r, HN2 or TEM will cause regression of enlarged mediastinal and cervical nodes. These patients may also respond to cortisone. The response of

these sensitive tumors is similar in many respects to that of chronic lymphatic leukemia and specific therapy should therefore be given cautiously. The resistant forms of lymphosarcoma, particularly the reticulum cell sarcomas, require much higher doses of x-rays to produce regression; the response may be prolonged, but often following a marked regression the disease recurs rapidly and becomes resistant to therapeutic doses of x-rays. These tumors also show a similar and very transient reaction to TEM or HN2, and these drugs are usually of little practical value in rapidly growing and resistant reticulum cell sarcomas.

Acute leukemia may respond to the adrenal cortical steroids, the folic acid antagonists (aminopterin and amethopterin) and 6-mercaptopurine (purinethol).[2] The most consistent and favorable results have been obtained in children. Mediastinal enlargement occurs in some patients, and these enlarged nodes usually regress during a hematologic remission of the disease. (Fig. 11, Case IX.)

Pulmonary problems are not prominent in chronic myelocytic and lymphatic leukemia. When pulmonary infiltration or mediastinal enlargement occurs, if the process is not controlled by appropriate specific systemic therapy, such as the use of HN2, TEM, myleran, P^{32}, urethane or 6-mercaptopurine, small doses of x-rays to the lung or mediastinum (200 r) may produce tumor regression. Lymphosarcomas in children are treated with x-rays and HN2 during the localized stage, but they may also respond to the same systemic agents effective in acute leukemia.

Children's Tumors. Many cancers of childhood produce pulmonary metastases. These include embryonal rhabdomyosarcoma, Wilms's tumor, Ewing's tumor, embryonal carcinomas and neuroblastoma. The histologic appearance of the tumor is not a reliable guide to radiosensitivity, and the temporary response to x-ray therapy may sometimes be remarkably good. These tumors in children, regardless of their extensive distribution in the lungs, are worth treating. Occasionally x-ray therapy is combined with a preliminary course of HN2.

Supportive Measures. While specific therapy offers the only chance of relieving the underlying disease, many major problems can only be managed by supportive measures.

Chest pain and cough are treated with opiates. Dyspnea is usually relieved only by successful specific therapy. However, pleural effusions, associated cardiac failure or associated pneumonitis may be aggravating factors which are amenable to supportive measures including thoracenteses, digitalization or antibiotics.

If the principal problem is one of endobronchial obstruction, antibiotics, expectorants, bronchodilators, hydration and postural drainage will help to eliminate the infection and mucous plug formation and the resultant atelectasis.

If anoxemia is present, oxygen should be administered either by nasal tube or in a tent. The possibility of respiratory acidosis should be kept in mind inasmuch as oxygen administration may be harmful in such situations. Respiratory alkalosis likewise can occur with the hyperventilation sometimes seen with extensive pulmonary infiltration. Treatment with a 5 per cent CO_2—95 per cent O_2 mixture may be helpful in respiratory alkalosis. These respiratory disturbances will be discovered only if thought of and if a CO_2 content of the blood is obtained. Occasionally the clinical picture and a CO_2 content are sufficient to make a diagnosis, but in some instances a blood pH may be necessary.

If the patient presents a picture consistent with cor pulmonale and right heart failure, the usual measures including digitalization and diuretics should be undertaken.

Pleural manifestations most commonly are those of fluid collection. Recurrent effusions present a very difficult problem in management. At present repeated thoracenteses combined with specific therapy constitute the best treatment. Bronchopleural fistulas and pneumothorax are likewise difficult to treat. Measures (talc insufflation) to induce an adhesive pleuritis around the lesion may be tried but are usually unsuccessful.

When the patient demonstrates the findings of superior vena caval obstruction, general measures should include salt restriction, diuretics and semi-recumbent position.

The miscellaneous group of complications (nerve paralyses, esophageal invasion, myocardial invasion, etc.) are treated best with specific measures. Occasionally pericardial paracentesis becomes necessary if tamponade due to effusion becomes a problem. Tamponade, however, may reflect extensive replace-

ment of the pericardium by tumor and paracentesis would be useless. Digitalis and quinidine or both may be of use in controlling arrhythmias.

SUMMARY AND CONCLUSIONS

Involvement of the respiratory tract by inoperable or recurrent bronchogenic carcinoma or by metastatic neoplasms is a common problem which almost always results directly in death or is associated with a fatal extension of the neoplasm elsewhere in the body. By a careful analysis of the pathogenesis of the pulmonary disturbance and the use of specific measures which may restrain the growth of the neoplasm, and by appropriate supportive measures it is possible to relieve symptoms, sustain morale, increase the period of useful life and occasionally prolong life. Favorable responses to treatment are to some degree unpredictable in the individual patient, and the physician is justified in pursuing an optimistic and aggressive therapeutic approach. The specific measures available include: (1) the application of local x-ray therapy; (2) radioactive gold in recurrent pleural effusions; (3) nitrogen mustard, triethylene melamine and related compounds in lung cancer, in selected cases of metastatic carcinoma and in the lymphomatous diseases; (4) hormonal control procedures in metastatic breast and prostatic cancer; (5) radioactive iodine in selected cases of metastatic thyroid cancer; and (6) the adrenocortical hormones, the folic acid antagonists and 6-mercaptopurine in acute leukemia.

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Radioisotope Therapy in Pulmonary Disease

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Artificial radioactive isotopes have been widely utilized in clinical investigations for nearly two decades. Yet of the more than ninety artificially produced radioisotopes presently available, only twelve have been found useful in the treatment of human illness. Of these only four (I-131, P-32, Au-198 and Co-60) are now being clinically utilized in the treatment of diseases of the chest, principally pulmonary cancer. Nevertheless, many palliative benefits have thus been gained. They may be measured in terms of relief from distress and disability, and occasional prolongation of useful and comfortable life.

Particularly in bronchogenic carcinoma is there an urgency for an exhaustive investigative study of every possible radiotherapeutic agent, because the vast majority of such patients, when first diagnosed, are already beyond hope for cure by surgical means. Radiation therapy is today shouldering the burden of treatment in the inoperable case to an increasing degree and is doing useful work in relieving suffering in a way which is not possible at present by any other means.

In this discussion we shall review the current role of radioisotopes in the treatment of pulmonary disease, describing the guiding principles of treatment, the clinical benefits to be expected as well as the hazards entailed. For this review we shall draw largely upon published reports from other radioisotope laboratories both here and abroad, as well as upon our own experience in this field.

The criteria for an "ideal" radioisotope suitable for use in the treatment of pulmonary disease, principally neoplastic, include: (1) prompt and selective localization in the diseased tissues (which must be radioresponsive); (2) optimum half-life, 14 hours to 14 days; (3) well understood biologic behavior—distribution, excretion and localization; (4) suitable radiation spectrum; (5) low toxicity; and (6) availability. It appears that I-131, P-32 and the colloidal suspensions of Au-198 and P-32, as presently employed, barely qualify as "ideal" therapeutic agents for internal administration in intrathoracic cancer.

The therapeutic applications may be considered in the following categories: (1) selective absorption (e.g., radioiodine in intrathoracic metastases from cancer of the thyroid); (2) macrophage phagocytosis (e.g., colloidal suspension of Au-198 and P-32 in treatment of malignant effusion), (3) physical placement (e.g., interstitial, transbronchial and intravenous applications of colloidal suspensions of radioelements in accessible neoplasms), (4) external radiation source (e.g., cobalt-60 gamma ray therapy for deep-seated bronchogenic carcinoma).

THYROID CANCER—INTRATHORACIC METATASES

Radioiodine Therapy (I-131). Although more than eight years have elapsed since radioiodine was first employed in the treatment of advanced thyroid cancer, a strictly investigative approach is still mandatory in each new case. Only primary tumors and their metastatic lesions which concentrate iodine are suitable for treatment, and these are encountered in less than 15 per cent of the cases. In our laboratory, for example, only three of forty-three individuals with inoperable thyroid neoplasms were found acceptable for aggressive treatment by virtue of their initial or induced concentration of I-131. Pulmonary infiltrations rarely give evidence of response. On the other hand, large mediastinal tumors regressed under treatment in two of our patients for two and three years, respectively. In one case a striking degree of rehabilitation was accomplished for a period of three years (Sorrentino, Roswit and Yalow[57]).

The failure of I-131 to concentrate in pulmonary, mediastinal or hilar metastases from an unknown source does not necessarily exclude the possibility of their being of thyroid origin. Only a small percentage of patients will show an uptake of a tracer dose in a metastatic lesion

before the remaining normal thyroid tissue is thoroughly destroyed by a heavy dose of I-131 or surgically removed. The thyroid-stimulating hormone of the anterior pituitary may then encourage the metastatic deposits to take up and retain significant amounts of radioiodine. The uptake may be further increased in some cases by administration of thiouracil or thyroid-stimulating hormone.

Because of the many limitations of I-131 therapy, no patient with pulmonary or mediastinal metastases from cancer of the thyroid should be denied roentgen therapy if isotope treatment appears unfeasible or ineffective. One of our patients has survived nearly ten years without diesease after roentgen therapy for far advanced adenocarcinoma of the thyroid. This patient when first seen had massive cervical, mediastinal and hilar metastases associated with a large right lower lobe parenchymal lesion. The clinical picture was further complicated by a fulminating superior vena cava compression syndrome. The patient has remained in good health for the past ten years, working regularly as a train conductor. (Mayer and Roswit.[38])

INTRATHORACIC TOXIC THYROID

Radioiodine Therapy (*I*-131). Mediastinal goiters of a toxic nature or retrosternal recurrences of Graves' disease are completely amenable to radioiodine therapy and few of them need operation. The isotope therapy of hyperthyroidism is so well established today and the literature so replete with discussions of therapeutic management that we need deal no further with this problem in the present report.

INTRACTABLE EMPHYSEMA

Radioiodine Therapy (*I*-131). Present treatment for intractable pulmonary emphysema and/or fibrosis is generally disappointing and frequently of only temporary benefit. Since one fundamental effect of chronic lung disease is a deficiency in the supply of oxygen to the body, Bercu and Mandell[5] thought it worth while to determine the effect of lowering the basal requirements of the tissues for oxygen by making patients with chronic lung disease relatively hypothyroid with I-131.

These investigators selected ten patients with intractable emphysema who had been treated repeatedly by conventional methods and were still markedly incapacitated either at rest or upon slight exertion. Since antithyroid treatment could not be expected to alter the fundamental pulmonary lesion, objective changes in lung function were not anticipated. Reliance was therefore placed on standard exercise tolerance tests and subjective changes. Patients were considered significantly improved if they were able to perform activities which previously were not tolerated because of dyspnea. Those who did not give evidence of increased exercise tolerance, even though they were improved subjectively, were considered as only questionably improved. Of ten patients thus treated and carefully evaluated, seven were found to be significantly improved, one was questionably improved and two had no benefit. A similar experience was reported by Levine,[35] with worth while benefit in nine of fourteen patients.

CHRONIC LEUKEMIA—PULMONARY MANIFESTATIONS

Radiophosphorus Therapy (*P*-32). It has long been known that rapidly proliferating tissue shows a more rapid rate of uptake of phosphorus than normal tissue. This is particularly true in leukemia, and forms the basis for an effective treatment modality (P-32) in chronic myeloid leukemias. Involvement of the intrathoracic nodes or infiltration of the lung is not uncommon in this disease entity. The pulmonary manifestations may share in the systemic and hematologic improvement which follow radiophosphorus therapy in the myeloid form of the disease. The intrathoracic lesions of chronic lymphatic leukemia, on the other hand, are best treated by means of roentgen therapy. It will be of interest to follow further developments in the Au-198 precipitate therapy proposed by Müller and Rossier[43] for lymphomas. Huge radiogold particles are delivered to the lung via the intravenous route by these investigators, creating a form of radioactive microembolic therapy.

MALIGNANT PLEURAL EFFUSIONS

Radiogold Therapy (*Colloidal Suspension—Au*-198). Recurrent pleural effusion intensifies the suffering of a large group of patients with inoperable carcinoma of the lung or pleura, both primary and metastatic. Repeated thoracentesis soon becomes complicated by pneumothorax or infection, further burdening the patient's already slender survival period.

The cause of the malignant effusion is still poorly understood; it may be the result of multiple cancer seedings or implants on the pleural membrane, tumor compression of drainage tracts, interference with the dynamics of fluid transfer across the pleural membrane, or any combination of these various factors.

Roentgen therapy and nitrogen mustard have occasionally been helpful in this problem but the results of conventional therapy have been generally disappointing. A radioisotope in colloidal suspension emitting energetic beta particles can be easily introduced into the pleural space, delivering superficial radiation to the pleural membrane without traumatizing the underlying lung or harming other critical tissues, such as the bone marrow. The insoluble colloidal particles are soon found on the serous membrane, largely phagocytosed by macrophages. Müller[43] first used zinc-63 to attain these objectives, but the half-life of this agent is extremely short (38.3 minutes). Hahn[18,19] found that a radiogold (Au-198) colloid satisfied the therapeutic criteria very well. This agent is now in use in hundreds of clinics both here and abroad. Reports of favorable clinical results have come from Andrews and his colleagues,[2,3] Clark and LeRoy,[11] Kent and Moses,[30,31] King et al.,[33] Seaman, Sherman and Bonebrake,[55,56] Storaasli et al.[58] and Walter.[62]

Physics. Au-198 is easily created in the pile by neutron-gamma reaction from an abundant parent, Au-197. It is economically produced in high activity and is readily converted to a metallic colloid of extremely stable form, quite amenable to autoclaving. The half-life of Au-198 is 2.7 days and the radiation spectrum contains a beta particle of 0.41 mev energy and a gamma ray of 0.98 mev. In the pleural membrane fully 95 per cent of the radiation effect is produced by the beta particles. The maximum range of the beta particle in tissue or water is 3.8 mm., but 90 per cent of the energy is dissipated in the first millimeter. The gold is supplied commercially in a suspension of colloid particles approximately .003 microns in size.

Biology. Metallic gold is insoluble in body fluids and practically all of the injected material remains in the pleural space. After injection it is flocculated in large aggregates upon the pleural membrane, resting principally in the macrophages. Its mode of action in the control of effusions is not yet clearly understood, but it is presumed that the effect of radiation on the superficial surface of the neoplastic tissue which may line the pleural cavity is of some importance. Other assumptions include: (1) impact of radiation on normal serous membrane, with alteration of the dynamic process of diffusion; (2) radiation effect on the small blood vessels in the serosa; and (3) destruction of floating cancer cells. Kniseley and Andrews[34] found uneven distribution on cavity surfaces. Most particles were phagocytosed, only a fraction remaining in the colloidal suspension, usually enmeshed in fibrin. Deposition in the regional lymph nodes was slight and inconsistent. Tracer studies in our laboratory reveal that the radiocolloid may remain in the pleural fluid for several days in some patients, without deposition on the pleural surface. In such instances little or no clinical benefit may be expected.

Pathology. A diffuse radiation pleuritis is produced, with inhibition of fluid accumulation. There is a fibrous thickening of the pleura varying widely in degree, with extensive adhesions and pocketing of the fluid after multiple injections. Radiation changes in the tumor are not prominent, being limited only to superficial areas (Kniseley and Andrews[34]).

Method. The material is received in a cherry-red colloidal suspension containing 10 to 25 mc. of Au-198 per ml. A thoracentesis is performed and most of the pleural fluid is removed. If a fibrinous or bloody sediment is found, some investigators lavage the pleural space because gold may be concentrated in this sediment instead of flocculating directly upon the pleural surface (Rubenfeld[54]). After the injection the patient is required to change position frequently to assure thorough distribution. In several cases we have utilized an automatic rocking-bed for this purpose. The dose level varies in different clinics, ranging from 50 to 150 mc. Despite the growing tendency to give single massive doses (about 150 mc.) Andrews and his group[2] prefer to give 75 mc. as the initial dose, to be followed by larger doses after several weeks.

Equipment. A variety of systems for intrapleural administration of radiogold has been reported (Andrews et al.,[2] Rose, Osborne and Stevens,[49] Taplits,[60] and Ter-Pergossian and Sherman[61]). In our own laboratory an apparatus has been devised which is simpler to handle than those previously described, and offers additional safety features for medical and

laboratory personnel as well as for the patient (Yalow and Cohen[64]). The operating principle is the transfer, without direct handling, of suitably diluted radiogold into the patient by the hydrostatic pressure of a siphon system. Since syringe pressure is not used to force fluids through the system, danger of blowouts is avoided. Ter-Pogossian and Sherman[61] have outlined in detail the necessary laboratory facilities and equipment required in receiving, diluting, administering and monitoring Au-198 according to the specifications of the Atomic Energy Commission. Several important handbooks on radioisotope handling are now available on request from the National Bureau of Standards, Washington, D. C.

Radiation Hazards. The entire administration procedure usually requires about three minutes, with the bulk of the radioactivity passing into the patient in about half a minute. The radiation received at 3 feet from the shielded bottle is less than 1 milliroentgen per hour per 100 mc. The radiation during the transfer itself is not readily measurable, since the time of transfer is so short. The physician who may wish to steady the tapping needle with a clamp would receive less than 10 mr. per 100 mc. to his hands while his body receives 7 mr. Others entering the room receive less. In fact, with this procedure, radiation from patient after treatment represents the only potential hazard. At intervals after the administration of the agent the patient is monitored with a portable rate meter. When 100 mc. are given, there is usually an activity of 50 mr./hr. at the edge of the patient's bed and 5 mr./hr. at 5 feet from the patient. (It is well to recall that the maximum daily permissible dose is 50 mr.) The patient must be at least 6 feet from other patients. A nurse is permitted to be within 2 feet of such a patient for a maximum of twenty minutes a day.[49] The time can be doubled after three days due to physical decay of the radioisotope.

Selection of Patients. The measure of success in this therapeutic procedure appears to be directly related to the maintenance of strict criteria in the selection of patients. Suitable patients for radiogold therapy are those in relatively good condition, likely to survive long enough to enjoy the benefits of treatment. Patients who appear to be getting rapidly worse or already in a preterminal state are not often helped. A simple tracer study over a period of several days may help in selecting those patients in whom the colloid is promptly flocculated on the serous membrane. Kent and Moses[31] have found that patients whose primary lesion is an adenocarcinoma are most difficult to palliate. The site of origin appears to have no material effect on the outcome. When bulky tumors are present, roentgen therapy should be more useful. Patients with serous fluid are more likely to be benefited than those with sanguineous effusions and much fibrin sediment (Rubenfeld[54]). In some clinics radiogold is instilled in the immediate postoperative period after pulmonary resection for cancer, in an attempt to destroy floating tumor cells or tiny pleural implants (Kent and Moses,[31] and Rose, Osborne and Stevens[49]).

Results of Treatment. In favorable cases the fluid becomes clear, contains less blood and fails to reaccumulate. Even in favorable cases there may sometimes be considerable lag between the administration of the isotope and the cessation of fluid formation. Andrews and his colleagues[2] mention the disappearance of malignant cells from the fluid aspirated from these cavities. When fluid is well controlled, patients experience a distinct improvement in general well-being. In forty cases reported by Seaman, Sherman and Bonebrake palliation was achieved in approximately one-half the number of patients. Favorable results have been documented by most clinics.[2,3,11,30,31,33,55–57,62]

Of forty-one patients treated by Kent and Moses,[31] pleural effusion was completely arrested in twenty-five cases (60.9 per cent). In nine other patients (21.9 per cent) the effusion was unquestionably checked, as demonstrated by the need for aspiration at much less frequent intervals. In this group the distribution of pulmonary lesions was as follows: bronchogenic carcinoma, twenty-eight cases; carcinoma of the breast, ten cases; pelvic cancer, two cases; sarcoma of abdominal wall, one case.

In our own preliminary experience with this agent most of the patients died of far advanced disease too soon for evaluation of treatment. The dose employed, 35 mc., is now generally regarded as inadequate. However, this group served well in the development of effective technics and in tracer studies.

Reactions and Complications. Severe impairment of blood elements has been rarely observed,[8] and such effects are usually transitory, followed by complete recovery. Systemic

radiation reactions are unusual even when doses of 150 mc. have been employed. There may, however, be evidence of distinct pleuritis, with friction rub, accompanied by pleural and diaphragmatic pain.

Limitations of Au-198. (1) Although the penetrating gamma radiation contributes about one-twentieth of the radiation effect in the pleura and provides an effective label, this component of Au-198 creates problems in personnel protection during the period of preparation, administration and in the post-injection period. (2) The patient himself emits gamma radiation and must be hospitalized and restricted as long as more than 30 mc. are retained in his body (United States Atomic Energy Commission regulations). (3) Large shipments over long distances from the commercial source become relatively expensive. (4) The half-life is too short. (5) Tissue penetration of the beta particle is too shallow. (6) Transfer of particles to pleural membrane is not consistent. These limitations and hazards of Au-198 therapy stimulated our interest in the use of a pure beta emitter with a longer half-life and more energetic beta particles. Radiophosphorus appeared to satisfy these criteria and a colloidal suspension of Cr P^{32} O_4 was prepared by the Abbott Laboratories under the direction of Dr. D. Tabern.

Radiopbospborus Therapy (Colloidal Suspension—Cr P^{32} O_4)—Advantages of Colloidal Cr P^{32} O_4. This agent has several theoretic advantages over radiogold, including: (1) longer half-life (14.3 days), most of the radiation being expended over a period of six to eight weeks, an optimum time interval in radiotherapy of most neoplasms; (2) more energetic beta particle, penetrating more deeply into tissue (maximum of 8 mm. compared to 3.8 mm. for Au-198); (3) absent gamma component, therefore greater safety, economy and convenience in shipping, handling, administration and management of the patient after treatment; (4) greater ionization and destruction action per disintegration; (5) hospitalization is not required; (6) the P-32 beta particle of average energy will affect a volume of tissue 50 times greater than that of the average Au-198 beta particle. Flocculation on the pleural surface is prompt and consistent. In the first eight patients studied there was prompt and almost complete disappearance of the material from the pleural fluid within less than twenty-four hours in every case, and in most cases in less than fifteen minutes. Good evidence has been presented that after injection most of the radioactivity remains on the walls of the injected cavity.[3] Doses of 15 to 20 mc. in less than 10 cc. of fluid were injected through the aspirating needle after most of the pleural fluid was removed. As in radiogold therapy, the patient was made to change position at frequent intervals after treatment.

Results of treatment in a larger series of cases will be discussed in a later communication.[52,53] It is of interest to mention that one patient, with intrathoracic lymphosarcoma and massive recurrent pleural effusion, unresponsive to conventional therapy, has remained fluid-free for nearly a year after intrapleural therapy with colloidal Cr P^{32} O_4. Jaffe[28] has obtained good results with this agent in approximately twenty of thirty patients with carcinomatous pleural effusion.

Colloidal yttrium-90, with a pure beta emission of high energy (2.18 mev) and half-life of 2.54 days, is being studied in several clinics for intrapleural and interstitial therapy. No clinical data are yet available.

INTERSTITIAL THERAPY

Extension of malignant disease to hilar and mediastinal nodes is frequently encountered at operation for bronchogenic carcinoma and represents the principal reason for failure to salvage the patient by surgical means. An effective method for intensive local irradiation of non-resectable nodes and other extensions of the neoplasm would be desirable at the time of surgery, to be followed by radical roentgen therapy. Radon seeds have occasionally been utilized by thoracic surgeons in this manner in an attempt to retard the malignant growth, but artificial radioactive sources are far more versatile.

Radioactive Gold Seeds (Au-198). Radioactive gold seeds of the required number and strength may be instantly cut to order in the operating room from previously irradiated gold wire. Gamma ray therapy is provided by shielding out the beta particles with gold tubing or sheathing.[24,45] British investigators have designed and utilized a new instrument in the form of an automatic gun for implanting radioactive gold seeds or grains into tumors with

great precision.[27] This instrument, as well as the platinum-filtered gold grains, is always available to the surgeon at the time of exploratory operation.

Radioactive Colloidal Gold (*Au*-198). Any well encapsulated, discrete neoplasm can be infiltrated with a radiocolloid beta emitter, as a means of delivering intensive ionizing radiation. Despite primary difficulties in achieving homogeneous infiltration and in dosage determination, radioactive gold (Au-198) may come to be a valuable adjunct in the management of advanced carcinoma of the prostate[32] and in the female pelvis.[56] It may well be applied to radiotherapy of inoperable bronchogenic carcinoma. The awkward, heavy, lead-shielded syringe generally employed to reduce the exposure to the operator can now be replaced by a pneumatic remote control precision injector for use in the operating room.[60] Radioautographic and roentgenographic technics have been developed to evaluate the effectiveness of the radiocolloidal localization in any site.[26]

Radioactive Colloidal Cr P^{32} O_4. Allen, Hempelmann and Womack[1] were the first to employ insoluble radioactive chromic phosphate in interstitial therapy of cancer (in experimental animals). We have explored its usefulness over the past two years in twenty-four patients with a variety of inoperable tumors including metastatic bronchogenic carcinoma.[51] In selected cases it may prove to be a valuable adjunct to roentgen therapy. The material can be safely handled in a conventional glass syringe shielded by a cylinder of lucite 10 mm. thick. Although an optimum dose level has not yet been established, tumor regression has been noted in a dose range from 30 to 100 mc. per gm. of malignant tissue. Injections are made in geometric patterns, simulating radium needle implantation. Forcible injection is avoided, the material being released as the needle is withdrawn. The findings in this study will be reported in a later communication.[51] It may be of interest that Jaffe[28] has noted tumor regression in eighteen of twenty-eight patients whose prostatic cancers were injected with radioactive colloidal chromic phosphate. A three-year arrest of a malignant mixed tumor of the tongue was reported by Mumma[44] after injection with this radiocolloid. A well documented experimental study of body distribution and tissue effects has recently been reported by McCormick, Milles, Jaffe and Seed.[40]

TRANSBRONCHIAL THERAPY

Meneely and colleagues[41,42] showed that when a colloidal suspension of Au-198 is given via the bronchus, the fluid vehicle is absorbed and the gold remains for many days in the lung parenchyma, delivering large doses at therapeutic levels. Lungs thus treated show striking gross radiation changes and the bone marrow is not affected. However, the gold colloid drains very slowly via the regional lymphatics, taking from ten to fourteen days to develop concentrations sufficient to permit adequate radiation of the lymph nodes. Since the half-life of Au-198 is only 2.7 days, it would thus appear to be less than ideal for irradiating the regional lymph nodes.

Silver-111 (half-life 7.5 days) was found by Hahn and his group[23] to be rapidly transported to the regional lymphatics after endobronchial administration, but this isotope is difficult to produce at the present time. Hahn and Carothers[20,21] then prepared a radioactive gold colloid (Au-198) coated with *inactive* silver which was removed from the lung parenchyma in considerable proportions, appearing promptly in the lymphatic nodes draining the particular lung region. Lymph node dosage was estimated to be of the order of 70,000 equivalent beta roentgens. Only negligible quantities of the material apparently gained access to the circulation. Surprisingly little radioactivity was found in the contralateral lobe. In every instance, however, there was drainage to the contralateral lymph nodes. This is particularly significant in view of the fact that unilateral primary lesions of the lung and breast are frequently associated with spread to lymph nodes on the contralateral side.

Since radiogold colloids remain in the lung parenchyma for long periods, and silver-coated radiogold colloids are transported to regional lymph nodes in high concentration, the possibility of utilizing both these agents in combination remains to be exploited. Hahn and Carothers[19] further propose the utilization of a gold isotope of a very high specific activity—Au-199 (half-life 3.3 days, with beta emission of 1.01 mev and gamma ray of 0.45 mev).

Bryant, Burke and Christophersen[10] were also able to deliver effective radiation to specific segments of the luug and to regional lymph nodes as well by direct instillation of radiogold colloid into a single lobe through the bronchoscope (using a urethral catheter) or by direct

injection into the submucosa of an intermediate bronchus by means of a long needle (through the bronchoscope). In the latter instance phagocytic activity carried the colloid through the lymph channels to the nodes. No liver damage was demonstrable in any of the animals. The authors suggest that a combination of these two methods may be a means of supplying radiation for palliation in patients with inoperable cancer of the lung involving hilar and mediastinal nodes.

INTRAVENOUS THERAPY

Selective fixation of a radioisotope in the human lung via the intravascular route was first accomplished by Müller and Rossier.[43] Zinc-63 was injected intravenously in the form of a non-soluble dispersoid sulfide, resulting in diffuse microembolism in the lung capillaries. This treatment was tolerated well, and in one patient a very large squamous cell carcinoma of the bronchus was reduced to a small fibrous rest. Radiozinc, however, has a very short half-life (38.3 minutes), which renders its general use unfeasible. Nor can the colloidal radiogold now widely employed for intrapleural use be utilized for intravenous therapy. The very small particles which make up this material (.003μ) will be passed through the lung capillaries to lodge in the reticuloendothelial system. Müller and Rossier[43] therefore utilized a radiogold *precipitate* of particle size 1,000 times larger than those of colloidal gold. The radiogold precipitate was thus localized within a single lobe of the lung by directing an intravenously introduced cardiac catheter (under roentgen control) into a predetermined pulmonary artery or a division branch. Calculated doses of 16,000 reps were thus delivered into the lung parenchyma.

TELECURIE THERAPY

Cobalt-60 (half-life 5.3 years) provides a powerful source of radiation equivalent to that produced by a 2 million volt x-ray therapy machine and can thus be employed as a substitute for the x-ray tube and generator. Such high energy radiation has brought tangible palliative benefits to patients with deep-seated cancer involving the thorax, abdomen or pelvis. Radiation in the range of 1 to 3 mev, when compared with conventional radiation (0.20 to 0.26 mev), has greater "reaching power" to the deep tumor and produces less skin reaction, less bone damage and little radiation sickness. The delivery of a more effective tumor dose now becomes feasible, with probable improvement in clinical results. The greater risks involved in more radical therapy in the region of the lung may possibly be ameliorated by the use of cortisone and ACTH (Cosgriff and Kligerman,[12] and Friedenberg and Rubenfeld[15]).

Cobalt-60 teletherapy units are rapidly coming into use in many clinics throughout the country. Fried,[14] in New York City, has treated more than seventy-five patients with inoperable lung cancer, employing one of the first cobalt-60 gamma ray units in this country. He states that the patients tolerated the treatment well, and the clinical results have definitely been improved compared with those achieved with conventional equipment.

Other useful nuclear sources of high energy radiation include iridium-90 (utilized in England), and cesium-137, now under consideration at Oak Ridge for release in the near future for telecurie therapy.

SUMMARY AND CONCLUSIONS

1. In this discussion we have reviewed the present role of radioisotopes in the treatment of pulmonary diseases, notably intrathoracic cancer, including the indications and guiding principles for therapy, clinical results to be expected and hazards involved. We have drawn largely upon the reported experiences of other radioisotope laboratories, both here and abroad, including our own experience in this field.

2. Of the more than 90 artificially produced radioisotopes now available, only four (I-131, P-32, Au-198, and Co-60) are today being clinically utilized in the treatment of pulmonary diseases. Nevertheless, the effort has been rewarding when appraised in terms of relief of distress and disability and prolongation of useful life.

3. A variety of applications of these versatile agents has been proposed for a joint attack upon the mounting problem of management of inoperable cancer of the lung. They include intrapleural, transbronchial, interstitial and intravenous technics for more effective delivery of the radiomaterial to the diseased tissues. A final evaluation of their therapeutic benefits, while not yet possible, will be awaited with great interest.

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Sarcoma of the Lung

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INCREASED interest and knowledge of pulmonary tumors in recent decades have altered many of the traditional concepts of these entities. At the turn of the century, for example, sarcoma of the lung was considered the most common primary pulmonary malignancy, but that was when lung tumors of any type were considered rare. Today, however, the picture is almost reversed. While bronchogenic carcinoma is recognized for its frequency, primary sarcoma of the lung is considered by some to be almost non-existent. It is a rare entity, occurring in a ratio of one in 7,272 autopsies from the University of Kansas Hospitals, an incidence of 0.014 per cent.[1] In 1936 Mallory[2] listed it among the rarest of tumors, reporting the first one in over 8,000 autopsies at the Massachusetts General Hospital. Since then, however, three more cases have been published from that institution. Reports of cases of sarcoma of the lung continue to appear in the literature[3,4] and it is probable that even more cases are seen which are not published. Whether this indicates an increasing incidence of this tumor cannot be determined at this time.

In a recent study of thirty-five cases of primary sarcoma of the lung[5] an attempt was made to define the clinical characteristics of this entity. The group included the following primary types: spindle cell sarcoma fifteen, fibrosarcoma six, lymphosarcoma five, osteoid chondrosarcoma one, mixed cell sarcoma one, reticulum cell sarcoma one, "round" cell sarcoma one, leiomyosarcoma one, chondrosarcoma one, plexiform sarcoma one, myosarcoma one and "sarcoma" one. No attempt was made to analyze the clinical picture for each of the various types of sarcoma. It was thought that while this may eventually be helpful and although reports by some authors[6] strongly support individual characteristics for some types, a larger number of cases will be necessary to evaluate this.

Probably the most significant consideration is to determine whether or not any distinguishing diagnostic characteristics can be found for sarcoma of the lung. To assay this, the clinical findings in patients with this type of tumor will be presented in comparison with the clinical findings in a representative collection of pulmonary carcinomas reported by Moore.[7] His cases represent the experience with bronchogenic carcinoma at the Presbyterian Hospital in New York City for the years 1940 through 1949.

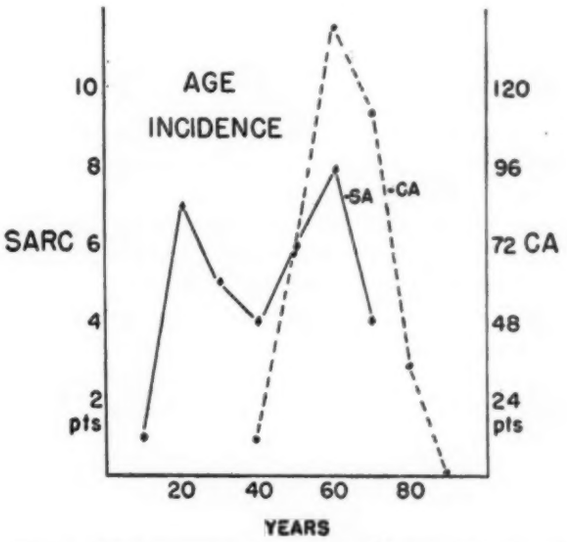

FIG. 1. The comparative age incidence of primary sarcoma and carcinoma of the lung.

Age. It has frequently been assumed that primary sarcoma of the lung occurs in the earlier decades. It is apparent that there is a difference in the age incidence of the two types of tumors, but considerable overlap occurs. (Fig. 1.)

Sex Ratio. It is suggested from Figure 2 that both types of pulmonary tumor are more common in males, although the preponderance is not so great in the sarcoma patients. Furthermore, in the sarcoma patients this apparent sex difference is not statistically significant in a series of only thirty-five cases.

Symptoms. In two of the patients with sarcoma of the lung there were no symptoms, the lesion having been found on routine roentgenographic study. One of these, a lymphosarcoma, replaced the entire left upper lobe. This was the only case in the series which

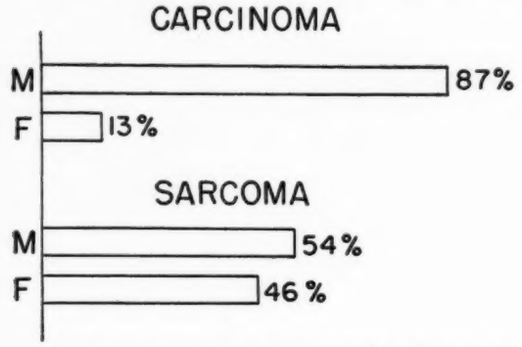

FIG. 2. A comparison of the sex ratios of sarcoma of the lung and bronchogenic carcinoma.

corresponded to what previous authors have described as the classic picture of sarcoma, a large, slowly growing silent tumor. The other silent mass, also a lymphosarcoma, was an isolated lesion in the right lower lobe and measured 8 cm. in diameter. (Table 1.)

TABLE 1
COMPARISON OF SYMPTOMS IN SARCOMA AND BRONCHOGENIC CARCINOMA

Symptoms	Carcinoma (Per cent)	Sarcoma (Per cent)
Cough	78	74
Hemoptysis	51	43
Weight loss	49	49
Chest pain	49	43
Fever	..	43
Pneumonitis	30	..
Weakness	20	26
Dyspnea	17	26
Wheeze	16	7

Roentgen Appearance. Chest roentgenograms of patients with sarcoma of the lung range from a perfectly normal roentgenogram through the many varieties of pulmonary tumor manifestations. In some cases the roentgenogram demonstrated no evidence of a tumor. In others solitary nodules, either regular or irregular in outline, large space-filling masses, atelectasis, cavitation, pleural effusion, pneumonitis, multiple densities, hilar enlargement, and in one case a mass containing calcium, were found. Tumor growth rate as determined by serial roentgenograms was of little or no value in differentiating this type tumor from bronchogenic carcinomas. The roentgen appearance, then, is not diagnostic and there is no consistent characteristic appearance of sarcoma in the lung.

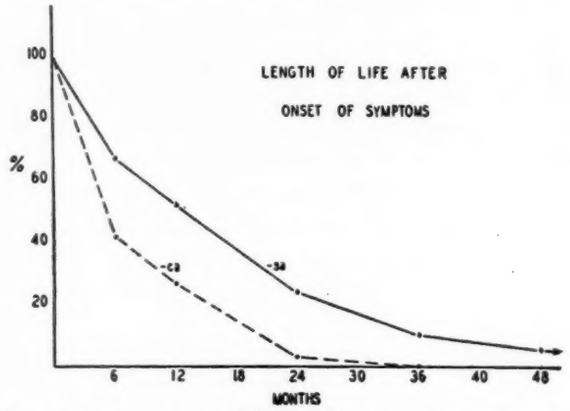

FIG. 3. A comparison of the total known length of symptoms in twenty-two patients who died of primary sarcoma of the lung with thirty-three cases of "untreated" bronchogenic carcinoma.

Longevity. Patients with primary sarcoma of the lung demonstrated a relatively greater longevity than did those with bronchogenic carcinoma. The one case of sarcoma graphed as still living at forty-eight months died fifty-nine months after the onset of symptoms. (Fig. 3.)

Treatment. Of the total thirty-five cases of sarcoma of the lung, eighteen or 48.5 per cent, were amenable to surgical procedures. This compares with 24 per cent resectability in Moore's series of bronchogenic carcinoma. It is to be noted that in four cases the tumor could be removed at thoracotomy without sacrificing lung tissue. It is also of interest that in two instances fulguration at bronchoscopy was at least temporarily adequate, and in a third the patient herself coughed up the tumor with no further evidence of the sarcoma four years later. Follow-up for various periods showed that 59 per cent of the postoperative patients were still alive.

Pathology. Of eighteen cases in which postmortem examinations were performed, metastases were found in ten and no metastases were found in eight. The distribution of these metastases included eight (one questionable) to the lungs; two each in the local nodes, kidney, spleen, and liver; one each in the brain, diaphragm and heart; and one (questionable) to the spine.

COMMENTS

The findings in thirty-five cases of sarcoma of the lung indicate that it is a rare tumor found only questionably more frequently in males than in females. It occurs equally in persons under and over forty years of age. The clinical picture and roentgen manifestations of this type of tumor can be quite similar to bronchogenic carcinoma. Surgical resectability of pulmonary sarcomas may be higher than for carcinomas of the lung. No distinguishing clinical characteristics to aid in the differential diagnosis have been found. Biopsy remains the only sure method of diagnosis.

TABLE II
SURGICAL TREATMENT

Procedure	No.	Living	Follow-up without Evidence of Recurrence
Lobectomy (one or more lobes)	5	2 1	14 mo., 6 mo. 2 yr. (with recurrence)
Pneumonectomy	6	4	7½ mo., 12 mo., 18 mo. and 36 mo.
Thoracotomy (with tumor removal)	4	4	19 mo., 15 mo., 7 mo., and ? mo.
Thoracotomy (without tumor removal)	1	0	.....
Craniotomy	1	0	.....
"Coughed tumor"	1	1	4 yr.
Died at surgery	2	0	.....
Bronchoscopy with fulguration	2	2	12 mo. and ? in 1 who also had roentgen therapy

A serious consideration with this type of tumor is the frequency with which sarcomas elsewhere in the body will metastasize early to the lung and mistakenly be interpreted as a primary tumor. Microscopically, the difference between the primary and the metastatic sarcoma may be extremely difficult. The slow-growing nature of sarcomas from several type tissues, notably bone, may make the primary source of such metastases frequently very obscure for long periods of time. The diagnosis of primary sarcoma of the lung then is best made when either a complete autopsy examination discloses no other source for the tumor tissue, or a sufficient period of time has elapsed to rule out biologically a primary source elsewhere in the body.

Mention should also be made of a particular type of sarcoma which is not included in these considerations. It is the so-called carcinosarcoma. True carcinosarcomas are single lesions with both carcinomatous and sarcomatous components found in the esophagus, uterus, larynx, bronchus and lung. Their metastases may show a microscopic picture of carcinoma only, sarcoma only or both. Bergmann, Ackermann and Kemler[9] have reported in detail two carcinosarcomas of the lung which they found in 258 surgically treated bronchopulmonary tumors at Barnes Hospital. They have also found four so-called "collision" tumors which were the result of chance intermingling of a carcinoma and sarcoma arising fortuitously close to one another and presenting a microscopic picture similar to carcinosarcoma.

SUMMARY

1. Primary sarcoma of the lung is a rare tumor, found only questionably more frequently in males than in females. It occurs in persons under forty as often as it does in those over forty.

2. A comparison of the clinical picture and roentgen manifestations of this type of tumor with those of bronchogenic carcinoma reveals no distinguishing characteristics.

3. The duration of the patient's life and the surgical resectability of pulmonary sarcoma may be greater than for carcinoma of the lung.

4. The frequency of slowly growing sarcomas elsewhere in the body which metastasize to the lung make it necessary to be cautious in diagnosis of a sarcoma as primary in the lung.

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The Pathology of the Lung in Hodgkin's Disease

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From the Dorothy H. and Lewis Rosenstiel Foundation, St. Vincent's Hospital Hodgkin's Disease Research Project. The work was also supported in part by grants from the Damon Runyon Memorial Fund.

IT is the purpose of this article to present a study of the pathologic changes produced in the lung by Hodgkin's disease and to describe the clinical symptoms resulting from such involvement. This will be followed by a discussion of its pathogenesis, a review of recent and current work on etiology and therapy, and finally concluded by remarks on the nature of the disease.

The clinical and pathologic data were obtained from forty patients followed up by us in the Hodgkin's Clinic of St. Vincent's Hospital. These patients subsequently died and were autopsied at the hospital. The control group was composed of forty-three other patients from the same Clinic dying from or with the same disease, and upon all of whom necropsy was performed.

Pertinent clinical data pertaining to these patients are found in Table 1.

Lung Pathology. Hodgkin's disease produces the following gross forms of pathologic disease in the lung: (1) discrete nodules resembling metastatic tumor (Fig. 1); (2) diffuse pneumonic involvement resembling lobar pneumonia (Fig. 2); (3) lobular, confluent lobular and bronchopneumonia types of Hodgkin's disease of the lung (Fig. 3); (4) a bronchitic type of Hodgkin's disease of the lung (Fig. 4); (5) a miliary type of Hodgkin's disease of the lung (Fig. 5).

The lesions varied from case to case as to number, size and distribution, and as a rule occurred mixed. Most common of these is the nodular form present as multiple, discrete, firm grey areas. Diffuse involvement of an entire lobe or portion of it is the second most common type, occurring seven times in our series. Although distal bronchioles and secondary bronchi are frequent sites of involvement by the disease under discussion, the main bronchi were affected less often—only 3 times. In one instance the lesion involved not only the bronchial tree but extended throughout the entire length of the trachea as well. The miliary form of pulmonary Hodgkin's disease is rare since only one example was found in our entire series of eighty-three autopsies.

TABLE 1

	Pulmonary Group	Non-pulmonary Group
Sex:		
Males	21	29
Females	19	14
Age distribution (yr.):		
10–20	10	1
21–30	4	9
31–40	14	13
41–50	8	8
51–60	4	6
61–70	0	6
Duration of life after Hodgkin's disease was discovered:		
Under 1 yr	1	10
1 yr	6	9
2 yr	13	9
3 yr	7	4
4 yr	2	3
5 yr	3	3
6 yr	2	2
7 yr	4	1
8 yr	1	0
10 yr	0	1
12 yr	0	1
15 yr	1	0

The pulmonary lesions were subject to a variety of degenerative changes such as cavitation, fistula formation and ulceration of bronchial lesions. The first was observed three times, the second once, and the third three times. In

FIG. 1. Nodular type. Note size, number and distribution of individual lesions. Lesions are firm, solid and grey.

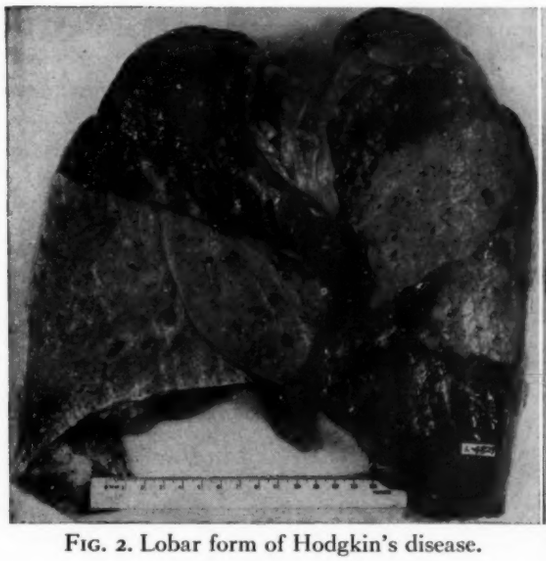

FIG. 2. Lobar form of Hodgkin's disease.

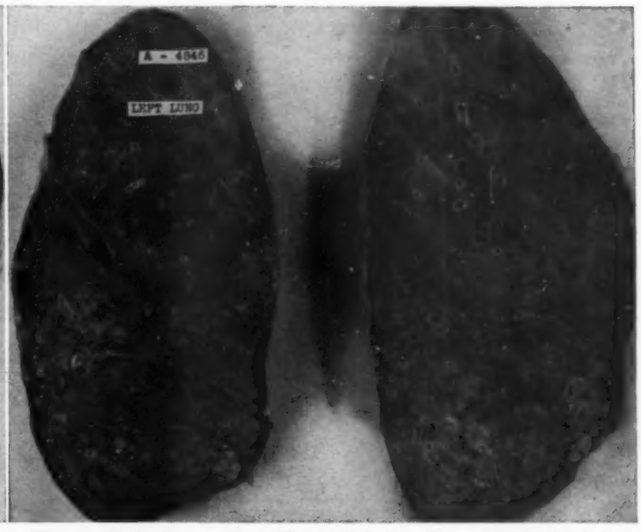

FIG. 3. Lobular and confluent lobular form of Hodgkin's disease.

one lung an entire lobe was reduced to a single cavity whose wall was composed of typical Hodgkin's tissue. A fistula occurred between this cavity, the trachea and esophagus. In two cases it was our distinct impression that excessive x-ray therapy may have been the cause of the cavitation.

In two lungs, in addition to Hodgkin's disease there was coexisting extensive tuberculosis. Cor pulmonale caused by extensive pulmonary Hodgkin's disease occurred once.

The pleura was affected twenty-two times by Hodgkin's disease, and in nine of these the lesions were limited to the diaphragm.

Pleural effusions were found in thirty-four of the eighty-three autopsies. Although pleural effusion frequently occurred when both lungs and pleura were affected by Hodgkin's, it was also seen when neither site was involved by it. Thus effusions were found concurrent with pulmonary and pleural involvement by Hodgkin's twenty times and occurred alone fourteen

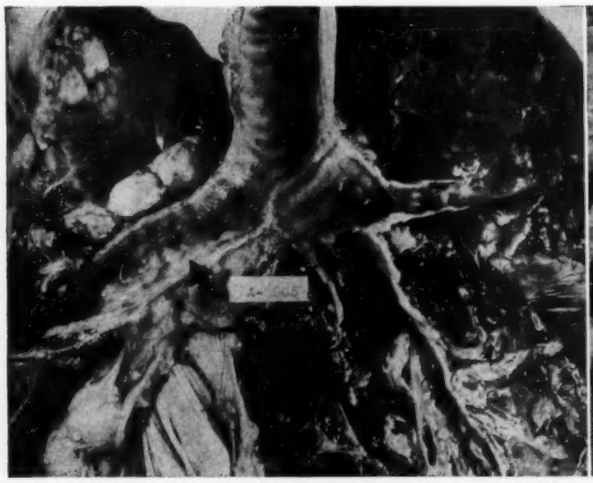

FIG. 4. Bronchitic type of Hodgkin's disease. Note the mucosa in the left main bronchus; it is raised and nodular.

FIG. 5. Miliary type of Hodgkin's disease. Note the uniformity of size and distribution of the nodules resembling miliary tuberculosis.

times. In nine instances Hodgkin's disease of the lung was uncomplicated by pleural effusion. The fluids were as a rule straw-colored and rich in fibrin. Only one of them was chylous. The quantities varied from 250 to 3,000 cc. The latter quantities produced complete atelectasis of the lung.

When the lungs are involved by the illness in question, mediastinal and hilar nodes are usually affected, too. Only in eight instances was this not so. There were many cases of mediastinal involvement with the lungs free of the disease.

In no instance was Hodgkin's disease limited solely to the lung. Always the latter was associated with involvement of many sites, i.e., liver, spleen, nodes, heart, etc.

While pulmonary lesions in comparison to extent of disease elsewhere were often small, they were at times sufficiently large to dominate the clinical picture.

Histologic Findings. In general the histology of Hodgkin's disease of the lung at autopsy, although complex, proved fairly uniform and was similar to that observed in the lymph nodes and other organs concomitantly involved by the disease. In all but one patient, who died from heart failure resulting from a rheumatic heart, the dominant cell was an irregular hyperchromatic reticulum cell mixed with fewer numbers of the Sternberg-Reed cell. In some cases the degree of cellularity was such that the picture could be called sarcomatous. Usually there was, however, a variable amount of fibrosis associated with the cellular proliferation. The Hodgkin lesion was to a large extent in and about the bronchioles producing typical bronchopneumonia. The process extended from here, into and about blood vessels, within interlobular septa, along alveolar walls and within acini. Thus complex pictures of lobular, bronchitic, bronchopneumonic and interstitial Hodgkin's pneumonia were produced. (Fig. 6.)

Of particular significance were the findings in the patient dying from heart disease, cited previously. Here the lesion was predominantly a lobular pneumonia. (Fig. 7.) The exudate present was chiefly lymphocytic with moderate numbers of reticulum and Sternberg-Reed cells. The same cellular pattern was observed in lymph nodes and other organs affected by Hodgkin's disease in this patient.

In addition to the typical Hodgkin's type of reaction, lobules were found filled with a fibrinous exudate, either pure or in a state of organization. Lobules distended with lipid engorged macrophages were common. The relationship and significance of both these lesions to the Hodgkin process is not yet known by us.

Clinical Aspects of Pulmonary Hodgkin's Disease. Although at times pulmonary symptoms dominate the clinical picture, the pulmonary lesion is often silent or obscured by symptoms arising from other organs more severely involved by Hodgkin's disease.

In a few instances the disease is ushered in by general symptoms of fever and malaise and the lung lesion discovered by x-ray in the ensuing

FIG. 6. A projection of a large section of lung. Note the discrete Hodgkin's lesion involving an area about a bronchus, pulmonary vessels and surrounding acini.

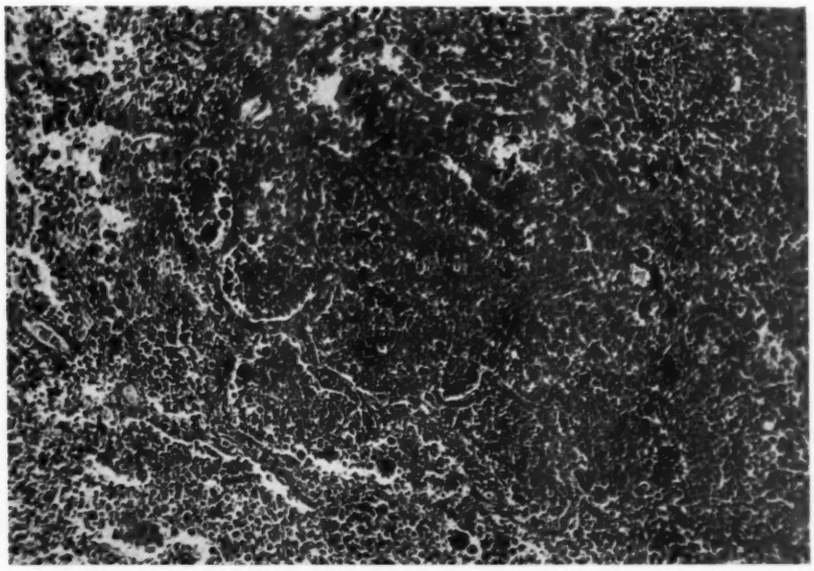

FIG. 7. Photomicrograph, hematoxylin and eosin stain, low power. Picture is that of lobular pneumonia. Exudate consists of lymphocytes and reticulum cells. Sternberg-Reed cells are conspicuous.

diagnostic work-up. In one instance in which symptoms of onset were pulmonary the work-up indicated lung tumor or suppurative disease, and a diagnosis of pulmonary Hodgkin's disease was subsequently established from study of a lobe removed at operation.

By far the most frequent experience is to discover pulmonary involvement by Hodgkin's during the course of the disease with the aid of the x-ray picture which it is our practice to take at three- to six-month intervals.

The common symptoms when they do occur

are cough, chest pain, and in advanced cases, dyspnea and orthopnea. The cough is usually dry and hacking. It can be severe, and when it persists into the night, interferes with sleep. The pain may be sharp or may be experienced as a "soreness or a heavy feeling."

Patients have survived for periods as long as four years after the lung lesions were discovered. During this interval, with the aid of x-ray pictures, the lesions have been seen to diminish in size, increase in size and change in shape. In no instance can we claim observing a lesion disappear completely.

Etiology. In the past ten years research into the etiology of Hodgkin's disease has been focused on a hypothetic microbiologic agent. In 1944 Grand[1] interpreted as indicative of the presence of a virus certain phenomena occurring in tissue cultures of Hodgkin's diseased nodes. This conclusion has not been concurred in by other investigators[2–4] who repeated the work. Both Hoster and Karnofsky attempted isolation of a Hodgkin's virus by inoculation of Hodgkin's diseased tissue extracts[5] or implantation of Hodgkin's material[6] on chorioallantoic membrane without success. Bostick[7] reports the presence in Hodgkin's material of an agent capable of producing a statistically significant greater mortality of embryonated eggs as compared to the effect of injecting non-Hodgkin's material. He extended his studies[8] and finds that this same material inoculated intracranially in suckling mice in due course is rendered sufficiently virulent to induce paralysis in mice.

In 1952 Fleisher[9] considered as possibly significant to Hodgkin's disease a diphtheroid microorganism. This work is reminiscent of contributions of earlier years by Bunting and Yates[10] who apparently were the first to have isolated a diphtheroid in Hodgkin's disease, and later, Cunningham[11] who concluded that the diphtheroid was an air-borne contaminant.

Attempts to date to reproduce the disease with microbiologic agents isolated from patients with Hodgkin's disease have proved fruitless.

Pathogenesis. The micropathology of Hodgkin's disease presents a definite pattern of slow development in some patients, more rapid in others. In general the pattern seen at any one time has been, in our experienee, fairly uniform so that the study of a node from one area gives a fairly good insight of the histology elsewhere. In its earliest form the enlargement of the lymph node is due chiefly to hyperplasia of the lymphocyte obscuring very often an occasional enlarged reticulum cell with a prominent nucleolus.[12] Progress in the pathology is characterized by hyperplasia of this type of reticulum cell and the appearance of more bizarre forms with pleomorphic nuclei, the Sternberg-Reed cell. In time both lymphocytes and reticulum cells begin to diminish while fibroblasts and fibrous tissue increase until the node becomes completely fibrous. In other instances, instead of atrophy of cells and fibrosis, the abnormal forms of reticulum cells proliferate quite markedly so that the pathologic picture resembles a reticulum cell sarcoma. In most terminal cases of Hodgkin's disease one finds in a node or organ a mixed pattern, fibrosis and sarcomatous change—the extent of each varying from node to node and from case to case.

It is our opinion that a similar train of histologic events occurs in the lung and that an appreciation of this fact is pertinent to proper management of therapy.

Therapy. Since the lung constitutes but one of many foci affected by this disease, treatment must be directed toward the individual as a whole. X-ray remains as it has in the past, a very useful tool for the treatment of localized Hodgkin's disease. One word of caution must be raised concerning its repeated use because a shadow observed in the roentgen film does not disappear or is not altered. Failure to do so may be due to the fact that the lesion is predominantly fibrous or else of a sarcomatous pattern therapeutically refractory to the x-ray. Persistence in this method of treatment can only damage overlying or adjacent normal tissue.

In addition to the x-ray, nitrogen mustard[13] and triethylene melamine[14] have proved to be most useful drugs in the management of Hodgkin's disease.

When the foregoing three modalities have proved ineffectual, we have found butazolidin®[15] most helpful in controlling symptoms such as pain, fever and malaise. In selected cases adenosine-5-monophosphate[16] has a highly specific effect on pruritus. Cortisone and ACTH sometimes help. In an occasional case aureomycin, terramycin,® penicillin and other antibiotics aid in controlling unsuspected intercurrent infections.

Nature of Hodgkin's Disease. The nature of

Hodgkin's disease remains difficult to comprehend. Judged by the increasing conspicuousness of the morphologically altered reticulum cell as the disease advances, it would appear to be a proliferative disease; yet in the early phases it is the lymphocyte which dominates the microscopic picture. Why this should be so is not known. The cause and significance of the transition of one cell type from dominant role to another remains to be discovered. One fact does stand out, i.e., that increasing refractoriness to therapy seems to coincide with diminution in numbers of lymphocytes. The reason for this and what is indicated thereby is a fascinating but unanswered question. Nor do we yet have an inkling into the function of the eosinophil which is so conspicuous at times in Hodgkin's disease.

Thus much work remains to be done before the etiology of Hodgkin's disease is discovered and its nature elucidated. Until these aims are achieved, much of the subtle pathology of Hodgkin's disease will remain difficult to explain and the search for therapy will continue to be empiric.

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SARCOIDOSIS

Pulmonary Sarcoidosis

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ALTHOUGH sarcoidosis is a systemic disease capable of affecting almost any organ, its intrathoracic manifestations have come to be recognized as having prime importance in both diagnosis and prognosis. In detecting sarcoidosis in its earliest phase the most common initial clue is the disclosure of symmetrically enlarged bilateral hilar lymph nodes by a film made in a mass chest survey. These surveys have shown that sarcoidosis in its clinically silent stage is by no means rare. Regarding prognosis, the type and degree of pulmonary involvement and the course which the lung lesions take largely determine whether the patient will recover or be left with a significant degree of pulmonary insufficiency and cor pulmonale. The number of patients who in time suffer from respiratory difficulties is substantial and such patients account for a high proportion of the fatalities which occur in sarcoidosis.

The toll of disability and death from chronic pulmonary sarcoidosis is reflected in our experience with 134 patients over a nine-year period. Seven deaths have occurred, six from sarcoidosis. For all six, pulmonary insufficiency was an immediate cause of death. Eighteen of the living patients are handicapped by dyspnea, and in six of these the symptom is severe enough to be almost wholly incapacitating. There is but one other organ in which sarcoidosis does comparable damage, namely, the eyes. Twenty-six of our patients suffered some loss of vision, and in six patients the result was blindness in one or both eyes.

DEFINITION

The most widely accepted definition of sarcoidosis is one which was adopted by the Conference on Sarcoid of the National Research Council in 1948,[1] as follows:

"Sarcoidosis is a disease of unknown etiology. Pathologically it is characterized by the presence in any organ or tissue of epithelioid-cell tubercles with inconspicuous or no necrosis and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The characteristic lesions may be replaced by fibrosis, hyalinization or both. Clinically the lesions may be widely disseminated. The tissues most frequently involved are lymph nodes, lungs, eyes, and bones, particularly of the extremities. The clinical course usually is chronic with minimal or no constitutional symptoms; however, there may be acute phases, characterized by a general reaction with malaise and fever. There may be signs and symptoms referable to the tissues and organs involved. The intracutaneous tuberculin test is frequently negative; the plasma-globulins are often increased. The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued chronic course of the disease."

DIAGNOSIS

The diagnosis of sarcoidosis is arrived at by correlating clinical and laboratory findings with a characteristic histopathologic structure—the non-caseating epithelioid cell tubercle. This structure, the so-called "hard" tubercle, also occurs in certain granulomatous conditions of *known* cause: tuberculosis, leprosy, histoplasmosis, beryllosis and brucellosis, among others. Those conditions must therefore first be excluded. The next step is to determine whether the clinical and laboratory findings are compatible with sarcoidosis.

Usually there is a fairly typical clinical picture. The patient is likely to be between the ages of twenty and forty. Often the patient first comes under observation because a chest roentgenogram has unexpectedly disclosed bilateral hilar node enlargement, usually with-

out but sometimes with disseminated pulmonary lesions. As a rule in early cases there are no symptoms and no abnormal physical findings. However, on investigation some patients are found to have palpable superficial lymph nodes and a recent history of erythema nodosum along with joint pains; parotid or lacrimal gland swelling; uveitis or hepatosplenomegaly. If there is also a relative cutaneous insensitivity to tuberculin and an elevation of the serum-globulin and calcium levels, the finding of the epithelioid cell tubercles in the tissue biopsy may be expected, and that closes the diagnostic circle.

When neither superficial lymph nodes nor cutaneous lesions are available for biopsy, other means are used to obtain tissue to verify the diagnosis. Needle aspiration of the liver has yielded the granuloma with a fair degree of frequency. Less successful have been "blind" biopsies of nasal and bronchial mucosa, bone marrow and muscle.

All those diagnostic procedures are gradually being superseded by the scalenus fat pad biopsy.[2] Frequently even when the supraclavicular areas do not contain palpable lymph nodes, epithelioid cell granulomas are found within the fat pad which contains lymphoid tissue in communication with the upper mediastinal nodes. The fat pad lies behind the clavicle between the scalenus anticus and sternocleidomastoid muscles. It is easily removed under local anesthesia through a small incision in the supraclavicular fossa. Carstensen[3] has reported on 200 scalenus fat pad biopsies in sarcoidosis suspects and found 60 per cent of them positive. This procedure is proving itself especially useful in early cases when the disease process is still limited to the thorax.

The Nickerson-Kveim Cutaneous Reaction. There remains a fair-sized group of patients who have sarcoidosis but who nonetheless present either atypical clinical features or tissue biopsies which are wanting in the characteristic histologic changes. It is especially for such patients that the Nickerson-Kveim intracutaneous reaction has been found helpful. A report concerning 200 patients who underwent the test has been published elsewhere.[4]

The test consists of intradermal injection of a heat-sterilized suspension of human sarcoid tissue and histologic examination of the site of the injection after four to six weeks. In a positive reaction a sarcoid-like granuloma is produced at the injection site. A large percentage of sarcoidosis patients with biopsy verification and a group clinically diagnosed as having sarcoidosis reacted positively to the test—86 per cent of the former and 85 per cent of the latter. Two patients of a "control" group numbering fifty-four patients with diseases other than sarcoidosis also responded positively to the test—an incidence of 4 per cent of false positive reactions. Biopsy of the injected site was considered an obligatory part of the test. Suspensions of normal lymph nodes and normal spleen failed to evoke positive responses. Foreign body reactions and nonspecific inflammatory changes sometimes interfered with the microscopic reading. Some experience is required for proper reading of the test. As the disease process regressed, the test result tended to become negative; but positive responses were encountered in a few patients whose illness had begun a decade earlier. The Nickerson-Kveim intracutaneous reaction was considered a useful confirmatory tool in the diagnosis of sarcoidosis. The time required for reading the test was not found to be too great a handicap in view of the fact that many of the tested patients had gone through months or even years of investigation without having a definitive diagnosis established.

With the high yield of positive scalenus fat pad biopsies and the satisfactory results with the Nickerson-Kveim reaction it becomes less and less necessary to perform an open lung biopsy or a mediastinal node biopsy to establish the diagnosis of intrathoracic sarcoidosis.

Patient Material. The analysis presented herein is based on observation of 123 patients with sarcoidosis who showed evidence of mediastinal node or pulmonary involvement at some point in their illness. These patients represented 92 per cent of 134 cases in whom a diagnosis of sarcoidosis has been made during the last nine years. Almost all of the patients were observed at the Mt. Sinai Hospital Sarcoidosis Clinic or in the hospital's wards.

For sixty-six patients tissue biopsy or autopsy verification was obtained; for fifty the diagnosis was a clinical one and was also confirmed microscopically by positive Nickerson-Kveim tests. The remaining seven patients had neither tissue biopsy verification nor positive Nickerson-Kveim tests, but the constellation of intra- and extrathoracic organ involve-

ment, course and outcome of the illness made sarcoidosis the diagnosis of choice.

Female patients outnumbered male patients seventy-eight to forty-five. There were seventy-three white patients and fifty Negro patients. The age of the patients ranged from twelve to fifty-five years. The average age was thirty-three years; 103 patients or 83 per cent were under forty years of age. Seventy patients had extrathoracic lesions of sarcoidosis at some stage of their illness, usually with multiple organ involvement.

The patients have been under observation one month to eighteen years. The average observation period was 32.7 months. Forty-nine patients were observed one year or less, fifty-one patients from one to five years, and twenty-three patients more than five years. In some instances early observations were carried out at other clinics or by referring physicians. Our long-term observations are still relatively scanty.

All patients were given a Nickerson-Kveim intracutaneous test. One hundred thirteen patients or 93 per cent had a microscopically positive response. Ten patients reacted negatively. Five of the ten were patients whose pulmonary lesions had already undergone fibrosis.

As expected, most patients showed tuberculin insensitivity. Only eleven reacted to a dilution of 1:10,000 O. T. or the first strength P. P. D. Five reacted to a dilution of 1:1,000 O. T. Thirty-two patients responded only to a dilution of 1:100 O. T. and seventy-five did not respond at all. In short, 107 patients or 87 per cent reacted weakly or not at all.

CLASSIFICATION OF INTRATHORACIC LESIONS BY STAGES

For a clear understanding of the symptomatology and course of mediastinal node and pulmonary sarcoidosis it is helpful to classify the presenting roentgenographic lesions according to a chronologic scheme wherever possible. A classification of intrathoracic sarcoidosis which has been found useful in the present series is shown in Table 1. Extrathoracic lesions require their own schemes of classification, which vary with the organ affected.

Three stages of intrathoracic sarcoidosis are recognized: the first stage, which may be described as early or florid; the second or transitional stage; and the third, late or fibrotic stage. It is not always possible to fit a given case into the scheme with ease and precision. This was especially true of our patients with mixed lesions which were placed in the transitional stage. Yet each stage seems to have its characteristic set of roentgen patterns, its symptomatology and eventual outcome.

In this series 109 patients were considered to be in the early or florid stage according to the findings of the *first* chest film available for assessment. Seven patients were already in the transitional stage, and seven others had reached the late or fibrotic state when first observed. Some of the early stage patients went into the second and third stage while under observation; hence the number in the later stages rose from fourteen to thirty-eight. Nevertheless, in this, as in most published series of patients with intrathoracic sarcoidosis, the patients with early or florid lesions continued to outnumber the rest. This is understandable since most patients with early lesions recover without ever entering the two later stages. From mass roentgenographic chest surveys and follow-up observations it may be postulated that a sizable number of persons in the general population pass through the early stage of sarcoidosis and then recover with the entire episode undetected.

1. The Early or Florid Stage

The early or florid stage may be subdivided according to three distinct patterns which appear in the chest films, as follows: (1) bilateral symmetric hilar node enlargement, with or without enlargement of the tracheobronchial and paratracheal nodes; (2) widely disseminated or localized fine miliary and occasionally gross miliary nodulation in both lung fields with hilar node regression or persistence; and (3) diffuse fluffy bronchopneumonic patches usually accompanied by some nodal enlargement.

1. *Bilateral Hilar Node Enlargement (Sixty-two Patients).* If there is a stage of sarcoidosis which precedes the hilar node enlargement, there is as yet no way to detect it. Usually the first nodes to show any abnormality are those of the bronchopulmonary chain. Often the paratracheal chain on the right side is enlarged as well; less commonly, the tracheobronchial nodes on either side. Figure 1 shows all of those nodes enlarged. The differential diagnosis lies between sarcoidosis on the one

hand and, on the other hand, malignant lymphoma and metastatic carcinoma.

Symptoms seldom stem from the enlargement of the hilar nodes. Twenty-nine patients, or almost one-half the sixty-two patients with nodal enlargement, first learned of an abnormal shadow in the mediastinum through a film made in a mass survey or during a periodic health examination. Eight other patients had a chest film made during an attack of erythema nodosum, at which time the enlarged nodes were first discovered.

The remaining twenty-five of these early-stage patients with nodal enlargements had symptoms related to other manifestations. Here diagnostic impressions ranged from rheumatic fever to mumps, infectious mononucleosis, malignant lymphoma, hypersplenism, tuberculous meningitis and hyperparathyroidism or chronic glomerulonephritis (the last two proved to be renal impairment caused by hypercalcemia of sarcoidosis.) There was even an instance when trichinosis was suspected because voluntary muscles were affected by sarcoidosis. In each instance it was the presence of bilateral hilar node enlargement that raised the suspicion of sarcoidosis which later was confirmed by appropriate investigations.

Extrathoracic involvement, either silent or symptomatic, may be present at the time when the enlargement of the hilar nodes is detected. Such generalization, involving peripheral nodes eyes, parotid glands and liver, apparently occurs at times very soon after if not simultaneously with the hilar node enlargement. This became apparent in a few patients in our series. These actually had had a normal film just prior to appearance of the hilar node enlargement, and so it was possible to date accurately the onset of both nodal enlargement and symptoms.

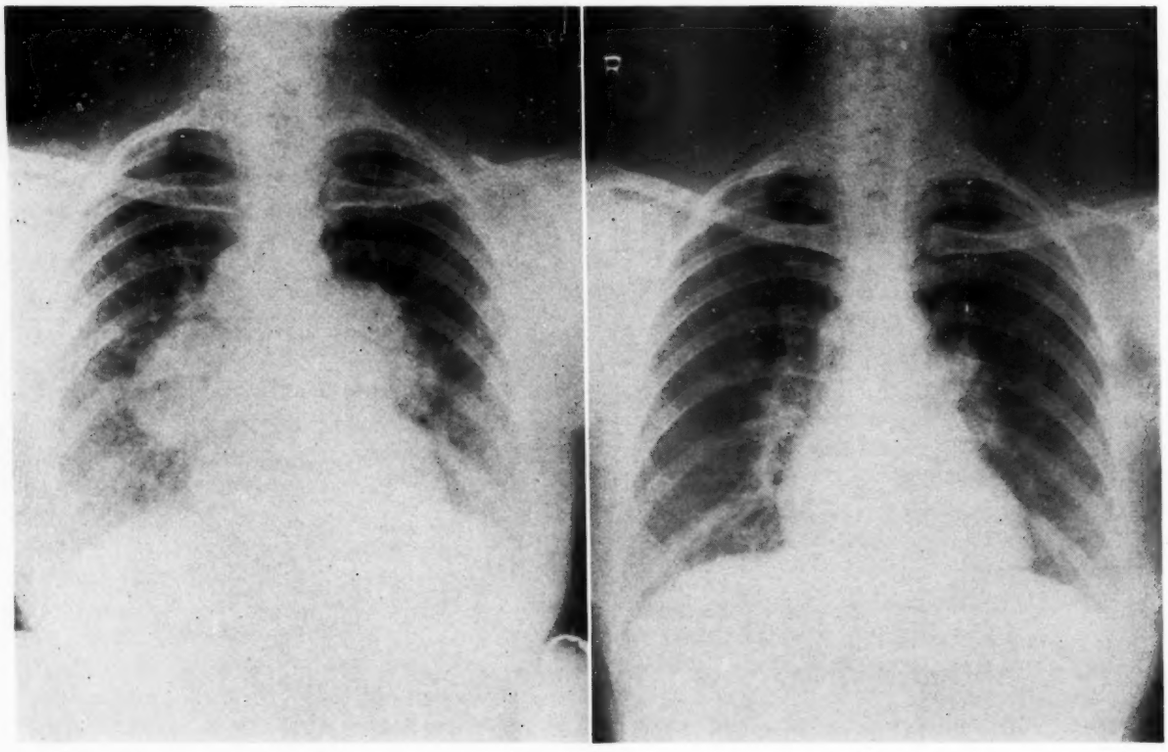
Although the pulmonary fields in this early nodal enlargement stage simply show a few perihilar streaks, there is indication that minute disseminated pulmonary lesions actually exist without being visible roentgenographically. This supposition is supported by the findings of Löfgren,[5] who had bronchoscopies performed on patients with bilateral hilar node enlargement ascribed to sarcoidosis. Among the bronchoscopic biopsies there were eight which had pieces of lung parenchyma attached to them, and four of these showed classical sarcoidosis lesions within the lung.

TABLE 1

COURSE OF SARCOIDOSIS (123 PATIENTS WITH INTRATHORACIC LESIONS)

Stage of Disease According to Chest Roentgen Pattern	No. of Patients in Specified Stage on *First* Film	Course of Lesions*				
		No. of Patients with Total or Nearly Total Regression	No. of Patients without Significant Change	No. of Patients with Progression to Fibrosis		Deaths from Sarcoidosis
				Transitional	Late	
I. Early or florid						
1. Bilateral hilar node enlargement	62	25	31	5	1	1
2. Miliary nodulation	33	7	13	7	6	2
3. Patchy infiltrations	14	4	4	1	5	1
II. Transitional: Reticular pattern plus nodules and infiltrations in pulmonary fields	7	0	6	6	1	..
III. Late or fibrotic: With bullae and non-specific infection	7	0	7	0	7	2

* Twenty-six patients with intrathoracic lesions received cortisone or corticotrophin therapy.



1A 1B

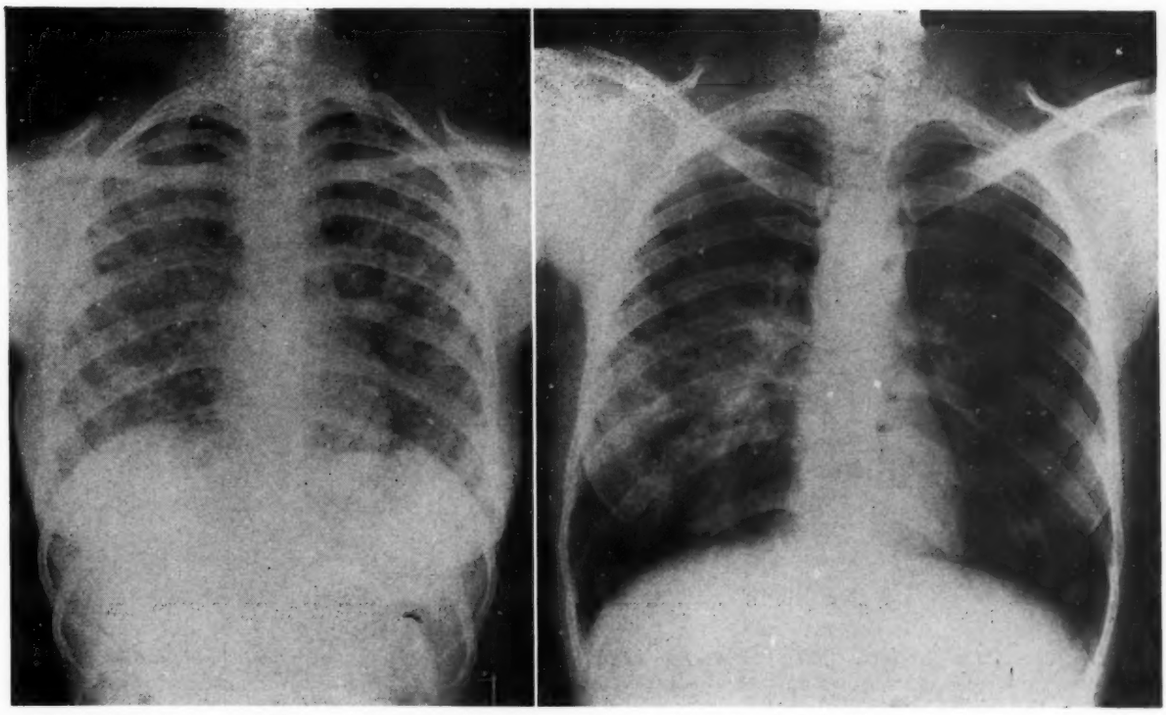
FIG. 1. A, chest film of a thirty-two year old woman with huge bilateral bronchopulmonary, tracheobronchial and right paratracheal nodes discovered through a survey film shortly before this film was made in December, 1947. Cervical node biopsy showed sarcoidosis. Nickerson-Kveim test positive; tuberculin test negative 1:100 O. T. B, film of same patient almost seven years later, October, 1954. Nodes remained enlarged for five years then suddenly shrank over the next two years. The right paratracheal nodes are still visible. Lung fields remained] uninvolved throughout. No respiratory symptoms.

Furthermore, impairment of pulmonary function occasionally is reported in patients with sarcoidosis with nodal enlargement only;[6,7] this, too, supports the idea that seeding of the lung is more common than is apparent on the film.

Course and prognosis: As Table 1 shows, the outcome of this stage of the illness is favorable. Of sixty-two patients who were followed up on the average twenty-seven months (twenty-eight patients for less than one year) there were twenty-five who experienced complete regression or nearly complete regression within the period of observation. Only one patient of this group experienced disabling pulmonary symptoms which led to death after fourteen years. Thirty-one of the group had persistently enlarged nodes. In many instances the nodes were smaller but still substantial. Sometimes the nodes remained enlarged for as long as five years before regression occurred. (Fig. 1.) With a longer period of observation many of the persistent nodes will disappear, if one is to judge by the adequately observed group. Löefgren[8] observed regression of nodes after two years in 72.6 per cent of seventy patients with hilar nodes. He has designated the enlargement of hilar nodes as the "primary" stage of pulmonary sarcoidosis.

Regression of the mediastinal nodes sometimes occurs at varying tempos in different chains. Occasionally the last to disappear are the right paratracheal or the left tracheobronchial nodes. Then the nodes are unilaterally enlarged and may be confused with enlargements caused by Hodgkin's disease and tuberculosis. Only three times in this series did a patient show unilateral hilar node enlargement, and in two of those instances the opposite bronchopulmonary nodes subsequently enlarged. Eight patients with erythema nodosum had complete resolution of enlarged nodes within two years.

In all, ten patients with hilar node enlargement later experienced pulmonary lesions.



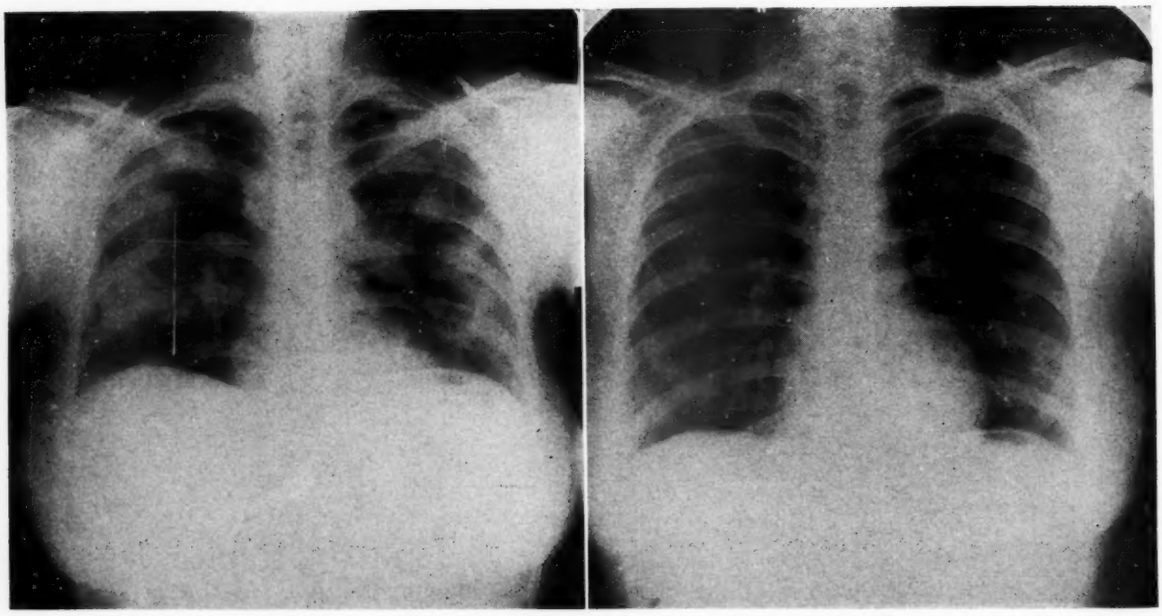
2A 2B

FIG. 2. A, chest film of woman twenty years of age with fine and coarse disseminated miliary nodulation bilaterally without apparent nodal enlargement discovered during pre-employment examination, September, 1954. Slight dyspnea on exertion. Scalenus fat pad biopsy showed sarcoidosis. Nickerson-Kveim test positive; tuberculin test negative 1:100 O.T. B, chest film of a twenty-eight year old woman with coarse and fine miliary nodules in lower half of the right lung field discovered through a survey film September, 1953. Left lung normal and no apparent nodal enlargement. Supraclavicular node biopsy showed sarcoidosis. Nickerson-Kveim test positive; tuberculin test negative 1:100 O.T. Several gastric cultures were negative for tuberculosis. There were no symptoms. No change in appearance of film during following year.

However, in four of the ten the lesions were of a miliary character and eventually disappeared without a trace; in the other six, fibrosis occurred. Five of the six patients eventually presented the reticular pattern of the transitional stage without symptoms and one, as stated, went on to dense fibrosis and death from pulmonary insufficiency. (Table 1.) A second patient in this group died but from an unrelated cause, gastric carcinoma. The death, not shown in the table, occurred eleven months after a biopsy-verified diagnosis of generalized peripheral lymph node sarcoidosis had been established. There were no symptoms of sarcoidosis.

In recapitulation, patients with bilateral hilar node enlargement seldom reach either the transitional or the late stage of chronic pulmonary sarcoidosis (in our series only six of sixty-two patients, or a little less than 10 per cent). Only one of these patients experienced dense pulmonary fibrosis with disabling symptoms, which led to death after fourteen years.

2. *Miliary Nodulation (Thirty-three Patients).* The roentgenographic pattern found here is characterized by widely disseminated fine miliary nodules. Probably this always follows enlargement of the hilar nodes although in some instances the nodal phase is missing, having gone by unrecognized. (Fig. 2A.) The miliary lesions may be unilateral (Fig. 2B) but this is uncommon. The miliary dissemination usually occurs within the same year as the hilar node enlargement, although exceptionally the nodulation first appears later. Sometimes the nodules are so fine as to give a ground-glass appearance to the lung fields, but usually they are slightly larger than those found in miliary tuberculosis—a condition which it strongly simulates on the chest film. The enlarged hilar nodes tend to grow smaller and disappear when the miliary seeding of the lung occurs, but some



3A 3B

FIG. 3. A, chest film of twenty-four year old housewife fluoroscoped during periodic health examination. Film was made April, 1950, and shows fluffy coalescent patches occupying large areas in the outer portions of both lung fields. Bilaterally enlarged bronchopulmonary nodes and right paratracheal nodes. Nickerson-Kveim test positive; tuberculin, histoplasmin and coccidioidin tests negative. Globulin 4.0 gm. per cent. B, film of same patient taken in February, 1951, ten months later, shows complete regression of lymph node enlargement and resorption of soft pulmonary shadows. Few areas of reticulation with scattered coarse nodules faintly visible—transitional stage. No symptoms or change in appearance of chest film during subsequent five years.

patients have persistent nodal enlargement throughout the phase.

Conditions which mimic this phase of early pulmonary sarcoidosis are, as mentioned, miliary tuberculosis, pneumonoconiosis, beryllosis, lymphangitic carcinoma, idiopathic pulmonary fibrosis and hemosiderosis complicating mitral stenosis, among others.

Miliary nodulation, like enlarged nodes, may cause no symptoms. However, low grade fever, fatigue and slight dyspnea are occasionally experienced. We have not encountered in this series acutely ill patients in the early phase whose complaint is tachypnea requiring an oxygen tent for its control. Such cases have been reported and they are found to have the alveolar-capillary block syndrome with gas diffusion difficulties.[7,9] Fourteen cases, or almost one-half of the thirty-three with miliary nodulation, were discovered through chest surveys.

Course and prognosis: These thirty-three patients with miliary nodulation on the first available chest film had a less favorable outcome than patients with hilar node enlargement only, as Table 1 shows. The thirty-three patients were followed up on the average thirty-eight months (twelve for less than one year).

Seven of the thirty-three experienced complete regression of the nodules. (If four other patients are counted who had miliary nodulation some time after discovery of hilar enlargement, then in our series there were eleven patients with miliary nodulation who had complete regression.)

Thirteen other patients had residual miliary nodulation but without respiratory symptoms. However, most of these were followed up less than two years.

Finally, the other thirteen of our thirty-three patients in time exhibited some irreversible pulmonary changes on the chest film. In seven of these reticular fibrosis of the transitional stage appeared; in two dyspnea occurred.

The other six of our thirteen patients, as the table shows, went on to the late stage of pulmonary fibrosis with formation of bullae, and five of them had considerable respiratory distress. Two succumbed to pulmonary insuf-

ficiency with cor pulmonale—one at the age of thirty-seven, seven years after discovery of the miliary nodulations, and the other at the age of thirty after eighteen years' illness.

In summary, of thirty-three patients whose first chest film showed miliary nodulation, thirteen later evidenced significant pulmonary fibrosis, of whom two died and five have respiratory difficulty. There was no way of predicting the outcome for the individual patient at the outset, but the later appearance of gross nodulation or coalescent patches was a bad omen.

3. *Diffuse Bronchopneumonic Infiltrations.* Fourteen of 109 patients of the early stage had an initial roentgen pattern of diffuse areas of soft mottling suggesting bronchopneumonic patches. These parenchymal lesions were usually accompanied by bilateral hilar node enlargement. (Fig. 3A.) The soft infiltrations are hard to differentiate from those of nonspecific bronchopneumonia, exudative pulmonary tuberculosis, eosinophilic pneumonia, acute beryllosis and terminal bronchiolar carcinoma, among others. In sarcoidosis the patient has very few or no respiratory symptoms, however, and the contrast between extensive involvement of the lung fields and the relative comfort of the patient may be taken as a hallmark of early pulmonary sarcoidosis. Six of our fourteen patients with patchy lesions were discovered in the silent asymptomatic stage by survey chest films.

The patchy infiltrations in the lungs appear to arise *de novo;* and if there is a stage of hilar node enlargement or miliary nodulation which precedes it, it must be extremely brief. In a few instances films were available from just before the film showing the soft lesions, and they were entirely normal. Although the patchy lesions do not appear roentgenographically to develop by confluence of miliary nodules, they may leave coarse nodules in their wake when they regress.

Course and prognosis: As can be seen in Table 1, the lung lesions regressed fully in four of the fourteen patients who started with this soft shadow manifestation of sarcoidosis. Four of the fourteen patients had persistent soft shadows, and two patients had dyspnea (one moderate and one severe). This last-mentioned patient, a fifty-six year old woman, succumbed to pulmonary insufficiency eleven months after discovery of her abnormal roentgen findings. Another of these patients showed remarkably rapid resorption of the infiltrations; within nine months only a few localized strands of fibrosis remained. The patient, a woman, had no symptoms during the succeeding four years and she has successfully passed through two spontaneous deliveries. (Fig. 3A and B.) In contrast, the table shows that five of the fourteen patients went on to dense pulmonary fibrosis. Two suffered from severe dyspnea and were totally disabled; one had moderate dyspnea.

In summary, of fourteen patients with an initial roentgen pattern of patchy bronchopneumonic areas, five were left with densely scarred lungs and one with a small localized area of fibrosis. Four were left with dyspnea. One patient of the group died of pulmonary insufficiency and cor pulmonale, her chest film at death still showing diffuse soft shadows and little evidence of fibrosis.

II. Transitional Stage

The transitional stage of intrathoracic sarcoidosis is characterized roentgenographically by fine or coarse reticulation. This network usually extends throughout both lung fields but it may be limited to a few areas. It is considered to be caused by infiltration of the interstitial tissue, particularly about the roots of the lung, with granuloma and fibrous tissue in varying proportions. In the background nodules and confluent mottled areas are seen. Occasionally the hilar nodes are still enlarged. (Fig. 4D.) Emphysema may be present but it is not so advanced as it is in the late fibrotic stage. Bullae are not a prominent feature. It usually requires two or more years to reach the transitional stage.

The roentgen picture of this stage of pulmonary sarcoidosis may easily be confused with the picture of diffuse pulmonary fibrosis caused by other conditions such as pneumonoconiosis, beryllosis, asthmatic bronchitis with infection, congestive heart failure, lymphangitic carcinoma and idiopathic pulmonary fibrosis of the Hamman-Rich type.

Only seven patients were placed in the transitional category originally, but it can be seen from the table that thirteen other patients passed from the early stage into this group and remained here for the rest of the period of observation, on the average thirty months. How-

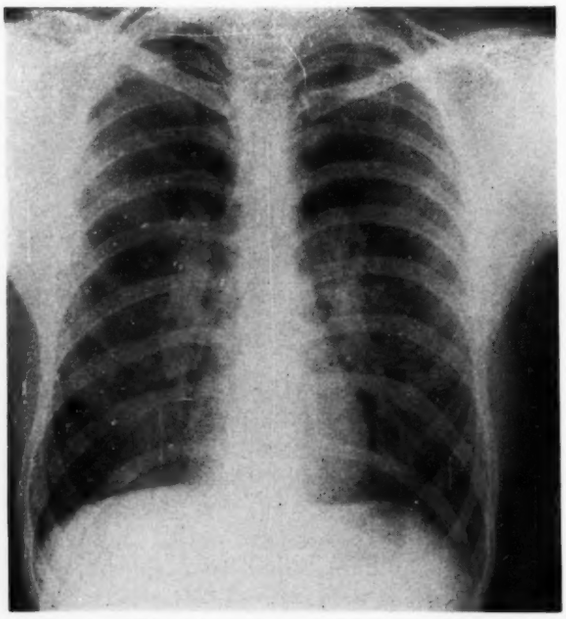


FIG. 4A. Film of a twenty-four year old man to have abnormal chest film during Army induction examination. No symptoms. Film made November, 1940, shows somewhat enlarged hilar nodes bilaterally with very fine miliary nodules throughout both lung fields. At tuberculosis sanatorium the patient was found to have negative reaction to tuberculin 1 :100 O. T. and was discharged. There was no history of industrial dust exposure.

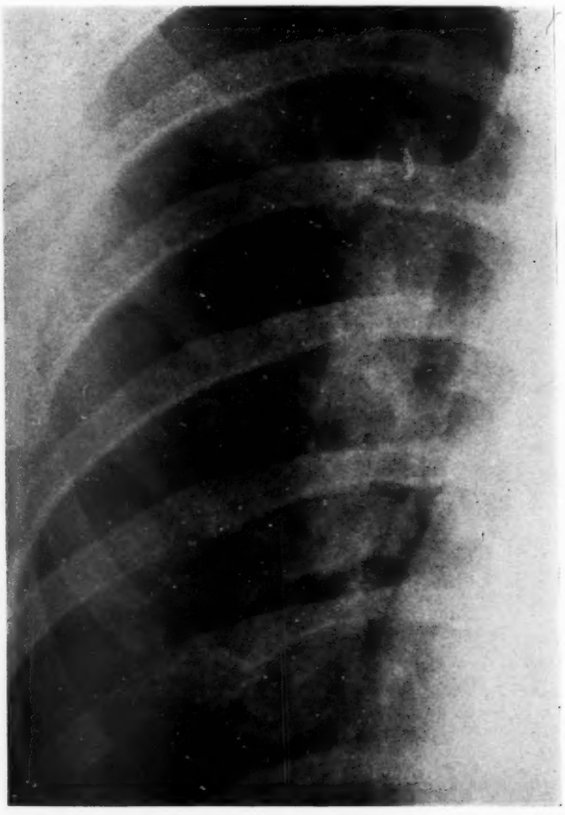


FIG. 4B. Detail of Figure 4A showing very faint miliary densities studding the lung field and enlarged right bronchopulmonary nodes.

ever, of the seven original patients in this category, six showed no change and one progressed to dense fibrosis. Four of the patients in this group had moderate dyspnea. Three patients had no symptoms at all in spite of significant changes in the lung fields. There were no deaths in this group.

III. Late or Fibrotic Stage

In the late fibrotic stage the granulomatous process in the lung undergoes involution and the lesions for the most part become hyalinized; the result is dense fibrosis and marked distortion of the normal roentgen pattern. Generally the extensive interstitial fibrosis, which is most pronounced near the lung roots and in the peribronchial and peribronchiolar regions, requires five years longer to come about. The roentgen pattern is characterized by retracted lung roots which are so dense that it is often impossible to recognize enlarged nodes when they are present. Coarse strands and nodules are mixed with finer ones and giant bullae may develop. (Fig. 4A to 4F.) Patchy infiltrations may represent non-specific superinfection.

Symptoms in this stage are usually severe. Dyspnea is outstanding. Cough and copious expectoration of purulent sputum may indicate a grave outlook. Hemoptysis occurs but infrequently. Some patients have marked cyanosis and clubbed fingers. Combined ventilation and diffusion difficulties occur. It may be difficult to differentiate the roentgen picture of this stage of pulmonary sarcoidosis from the picture which is seen in advanced bullous emphysema from any of numerous causes. However, the degree and extent of root fibrosis is seldom matched elsewhere. Chronic fibroid tuberculosis and third stage silicosis may come into the differential diagnosis.

All seven patients in this group had dyspnea. In three the complaint was disabling; in four it was moderate. Two patients died (aged thirty-four and thirty-eight, respectively) five years after discovery of lesions which were in

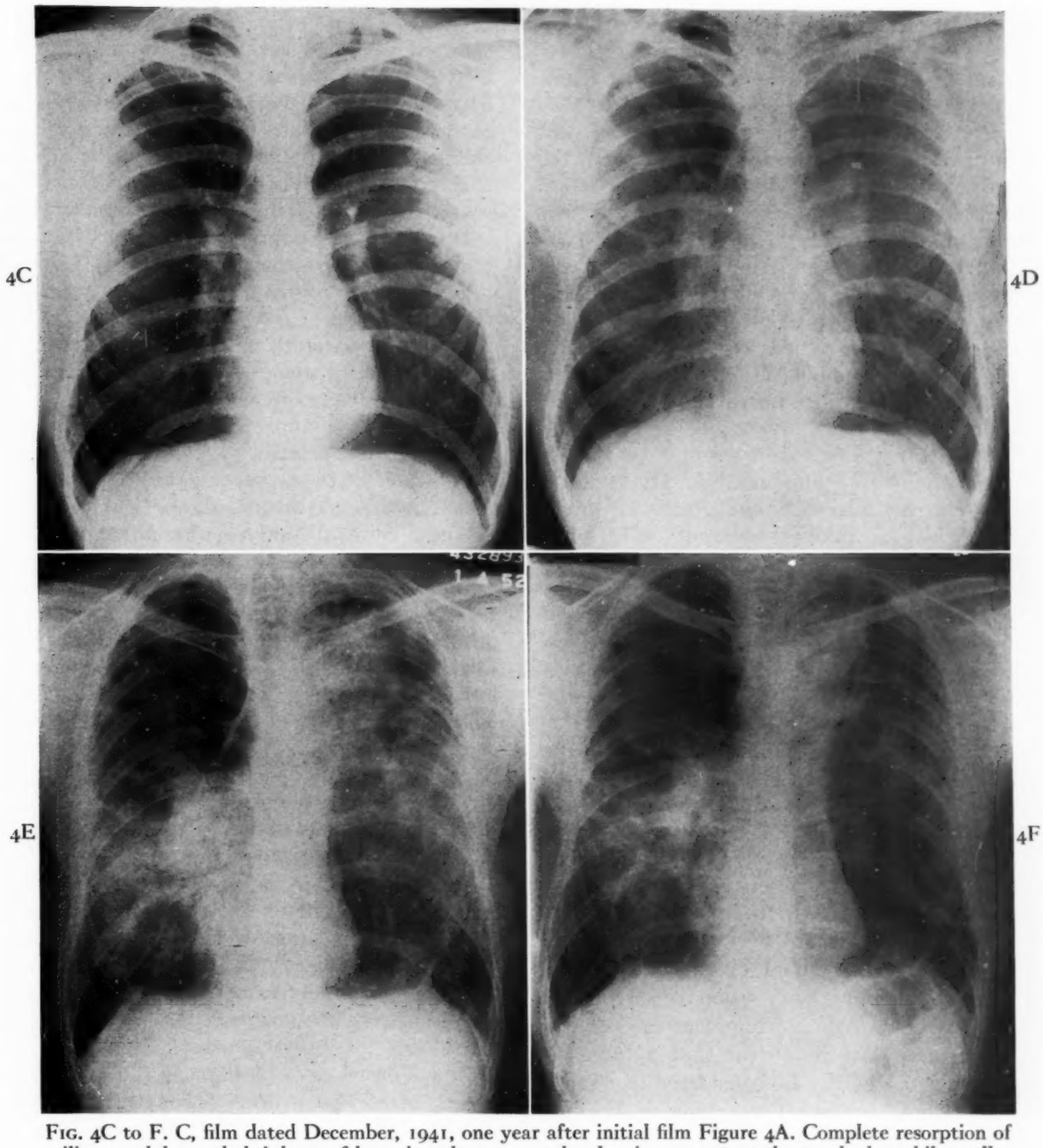


FIG. 4C to F. C, film dated December, 1941, one year after initial film Figure 4A. Complete resorption of miliary nodules and shrinkage of bronchopulmonary nodes, leaving accentuated root shadows bilaterally. D, film dated July, 1943, about two and a half years after initial film. The bronchopulmonary nodes are again enlarged and a reticular pattern is present in both lung fields. Faintly visible in the background are coarse and fine nodular densities—transitional stage. Still no symptoms. E, film dated January, 1952, eleven years after initial film. Gradually increasing fibrosis with coarse nodulation and coalescent shadows with formation of huge system of emphysematous bullae occupying upper half of right lung field—late or fibrotic stage. Increasing dyspnea for five years with severe respiratory distress at rest. Right lung root depressed by pressure of bullae. Left lung root pulled upward by fibrotic scarring. Nickerson-Kveim test positive; tuberculin test still negative. Repeated gastric cultures negative for tuberculosis. Globulin 4.8 gm. per cent. F, film dated October, 1952, two months after treatment with corticotrophin and cortisone with marked symptomatic improvement. Comfortable on maintenance cortisone therapy for the following two years. Some clearing of the soft shadows in the right lower and left upper lung fields. Bullae are unchanged.

each instance densely fibrotic. It can be assumed that they had had sarcoidosis for many years before the disease process became recognizable.

In conclusion, it is apparent that the outcome of intrathoracic sarcoidosis may be predicted on the basis of the roentgenographic pattern which is present when the patient first comes under observation.

It has been shown that patients exhibiting mediastinal node enlargement without parenchymal involvement (62 of 123) fare very well; only one of these patients died and only five were left with some residual fibrosis without disability. The average observation period was 32.7 months, which is relatively short; longer observation may increase the toll.

The other two groups of the early or florid stage had parenchymal involvement on initial films and these patients did not do so well. Of thirty-three patients with miliary nodulation, thirteen showed progressive fibrosis. Two died and five were left with dyspnea. Of fourteen patients with bronchopneumonic onset, six showed residual fibrosis and four of these patients were dyspneic. Among the fourteen there was one death.

Adding the deaths and disabilities of the patients of the transitional and late fibrotic stages, it is found that for the entire series of 123 patients seven died, six or 5 per cent of sarcoidosis; thirty-nine patients or 31 per cent showed evidence of irreversible pulmonary scarring; and eighteen patients or 15 per cent were left with significant respiratory disability.

Tuberculosis developed in three other patients after the pulmonary lesions of sarcoidosis had regressed. All three were Negroes.

From these data it is clear that pulmonary sarcoidosis can hardly be considered as benign in its outlook. Nitter's[10] searching analysis of ninety cases demonstrates this graphically.

TREATMENT

Before the advent of cortisone and corticotrophin therapy no treatment was demonstrably effective in sarcoidosis. It has been shown previously that cortisone therapy was capable of suppressing some clinical manifestations of sarcoidosis in thirteen patients.[11] Fresh lesions proved more responsive than older ones. The drug's suppressive action often proved temporary but even this was beneficial in selected instances in which the unremitting course of the disease was producing loss of organ function. Biopsies of various tissues removed during and shortly after cortisone therapy frequently showed regression of epithelioid cell tubercles and their replacement by scar tissue. The changes were similar to those occurring with spontaneous healing but the tempo appeared to be accelerated by the drug.

Since the previous study twenty other patients have been given the hormones.* Thus thirty-three patients in all have been treated in the last four and a half years, and a brief summary of the experience follows.

The sites of involvement for which hormonal therapy was *primarily* given were: lungs, twelve patients; eyes, seven patients; cutaneous or subcutaneous lesions, six patients; grossly enlarged cervical lymph nodes, three patients; central nervous system involvement, two patients; recurrent parotid swelling, one patient; severe arthralgia accompanying erythema nodosum of early sarcoidosis, one patient; and, finally, protracted fever and marked weight loss, one patient. Of the thirty-three patients who were treated with cortisone, diagnosis was confirmed by tissue biopsy in twenty-eight patients and by positive Nickerson-Kveim intracutaneous test in five patients.

Of the patients with pulmonary involvement, only those having moderate or severe dyspnea, twelve in number, were chosen for treatment. Patients with bilateral hilar node involvement and those with miliary nodulation were not considered to require therapy since they presented no pulmonary symptoms and the prospect for spontaneous recovery was considered good, particularly for the nodal group. Yet, as will be shown, the incidental effects of cortisone upon lesions of this type could be observed in a number of patients who were treated for lesions at other sites such as ocular and cutaneous sites. The duration of treatment usually ranged from four weeks to four months. Seven patients received more than one course. In three instances the treatment courses lasted forty to sixty-six weeks, and one other patient has been receiving maintenance cortisone therapy for the last two and a half years.

* Cortisone used in this study was partly supplied by Merck & Co., Inc.

The roentgenographic response to cortisone therapy of intrathoracic lesions varied. Accelerated clearing was the rule in patients with early stage pulmonary involvement. These lesions are known to revert spontaneously. Little or no roentgenographic clearing occurred in patients with transitional or late fibrotic stage pulmonary lesions. For that group the benefits which accrued from therapy were mostly symptomatic, as was expected.

The results of cortisone therapy according to the stage of disease at which the patient was treated follow:

Nineteen patients had enlarged mediastinal nodes; three of these showed complete regression, eight partial regression, and eight no change. The lack of shrinkage was noted often at the same time as the patient's peripheral lymphadenopathy disappeared dramatically. There was no relapse after the drug was stopped. As mentioned, in no instance was the basis for therapy the enlarged nodes.

Six patients had miliary nodulation of the lung fields; four of these had prompt and complete clearing, one partial clearing, and one no effect after four months' therapy. Relapse was uncommon; only one patient had recurrence of the nodules within six weeks after the drug was stopped. None of the patients was treated primarily for these lesions. In one, treatment was for a complicating bronchial involvement;[11] in five, for extrathoracic lesions.

Two patients had bronchopneumonic patches of early sarcoidosis, both complaining of dyspnea, and they experienced partial clearing of the lung infiltrations and lost their symptoms. One of these two patients had roentgenographic and symptomatic relapse five months after withdrawal of the drug. The other maintained gains but the period of observation is as yet too brief to determine whether the beneficial result will endure.

Three patients had transitional stage lesions in the lung and none of these showed much resorption on the chest film. Two of these patients had dyspnea and they had a good symptomatic response. The other patient received a drug for a central nervous system lesion and had no pulmonary complaints. The two patients who gained relief of symptoms from cortisone had prompt symptomatic relapse after the drug was discontinued.

Finally, seven patients had lesions of the late fibrotic stage. Of these, four showed no change on their chest films and three showed some lessening of infiltrations. One of these patients had no relief of dyspnea, cough and expectoration, and another died of a suppurative fungal infection while being treated with cortisone and antibiotics. Four patients who improved suffered prompt relapse after the drug was withdrawn, but one patient has continued on maintenance therapy for more than two years without relapse. The long-term result of therapy in this group has been unsatisfactory but this therapy is the best that can be offered at present.

Comment on Cortisone Therapy. In this series only those patients who were headed inexorably toward pulmonary insufficiency were treated with cortisone. It was realized that the drug could have no effect upon the scar tissue already present in the lung; yet in some instances patients with late fibrotic disease experienced considerable relief of symptoms. It is generally agreed that mediastinal node enlargement *per se* does not require treatment since in almost all instances spontaneous regression, even if slow, will eventually occur. Furthermore, there is also little question that the unusual patient with the picture of acute pulmonary insufficiency from diffuse miliary nodulation or bronchopneumonic patches of the early stage requires the hormone to tide him over the life-threatening period.

The unanswered question regarding cortisone therapy is whether or not to treat patients with early diffuse nodulation or infiltration before symptoms appear. If the patient is treated with hormones, pulmonary insufficiency may develop sooner because of the fibrosis-promoting action of the drug. We have seen fibrosis proceeding while the patient was receiving the hormones. If the patient goes untreated, he may continue to elaborate granulomatous lesions in the lung which eventually will make for a more severe pulmonary insufficiency.

More data about the rate of development of fibrosis and the resulting impairment of lung function will have to be obtained in treated as well as untreated patients before a valid conclusion concerning this problem can be drawn. The experience with this series of patients does demonstrate that in a good many instances early lung infiltrations caused by sarcoidosis, even though asymptomatic, later lead to a crippling of respiratory function.

In addition to these indications for cortisone

treatment of intrathoracic sarcoidosis, the following criteria are those presently observed for assessing the need for hormonal therapy for extrathoracic lesions of sarcoidosis: (1) in all cases with ocular manifestations, no matter how minimal; (2) patients with febrile course and marked weight loss; (3) patients with central nervous system or cardiac involvement; (4) patients with disfiguring cutaneous and superficial lymph node lesions; and (5) patients with persistent hypercalcemia. It appears that cortisone therapy can reduce the serum-calcium level and this may help prevent nephrocalcinosis and renal insufficiency. Moderate peripheral lymph node enlargement, parotid lesions and other minor sites of involvement generally do not require therapy.

Cortisone therapy is by no means a complete treatment for sarcoidosis. Perhaps when the etiologic agent is identified, a more direct approach to treatment may be possible.

In none of the thirty-three cortisone-treated patients in this series did tuberculosis develop. Carstensen[3] states there was no case of tuberculosis in his group of sixty-six patients with sarcoidosis who had received cortisone and corticotrophin.

SUMMARY

During the last nine years 123 patients with intrathoracic localization of sarcoidosis have been observed. There were six deaths from sarcoidosis. Thirty-nine patients showed varying degrees of pulmonary fibrosis, and eighteen patients among the survivors were left with significant respiratory difficulty.

Intrathoracic lesions could be assigned to one of three broad chronologic stages according to the roentgen pattern present on the initial chest film: early, transitional and late. In the early stage, for those patients whose film showed enlarged mediastinal nodes without pulmonary lesions the outlook was best. It was not so favorable for patients whose films showed miliary nodulation of the lung fields and still less favorable when the film first showed a patchy bronchopneumonic pattern. Patients in the transitional and late fibrotic stages often showed disabling symptoms, and five of the six deaths caused by sarcoidosis were in patients with pulmonary lesions in these stages.

Scalenus fat pad biopsies and the Nickerson-Kveim intracutaneous reaction are valuable diagnostic aids when involved tissue is not easily accessible for biopsy verification.

Cortisone and corticotrophin generally act favorably upon intrathoracic sarcoidosis although the benefits usually prove temporary. In severe pulmonary insufficiency occasionally seen in the early stage and more often in the late fibrotic stage of pulmonary involvement, hormones may be the only means to tide a patient over the crucial period.

In early stage lesions consisting of mediastinal lymphadenopathy, treatment is unnecessary because spontaneous regression is the rule. It is still debatable whether patients with asymptomatic miliary nodulation or bronchopneumonic patches in the lung fields should receive hormonal therapy in an attempt to forestall widespread pulmonary fibrosis.

In chronic pulmonary sarcoidosis the effects of the hormones are variable. Sometimes symptomatic relief is dramatic and sustained. More often the relief is partial and relapse occurs promptly after the hormones are withdrawn. Pulmonary fibrosis may proceed even while the patient continues to receive the drugs. Indications for the treatment of extrathoracic lesions of sarcoidosis are listed.

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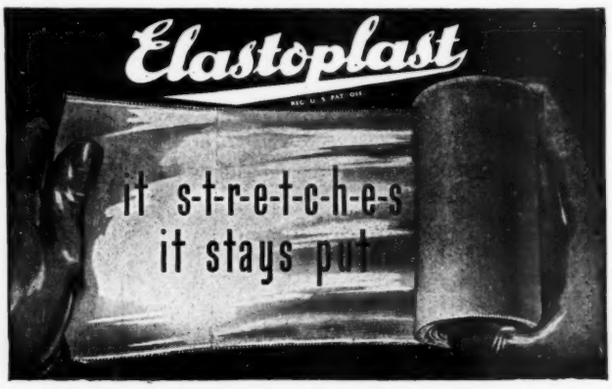

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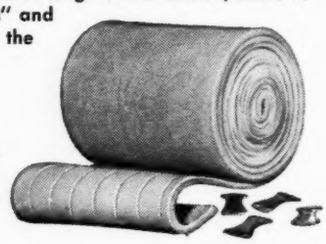

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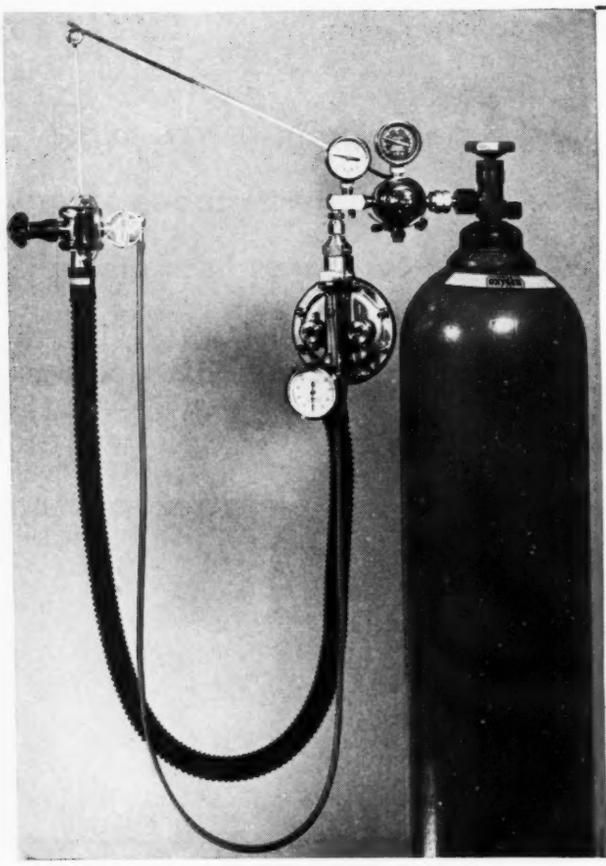

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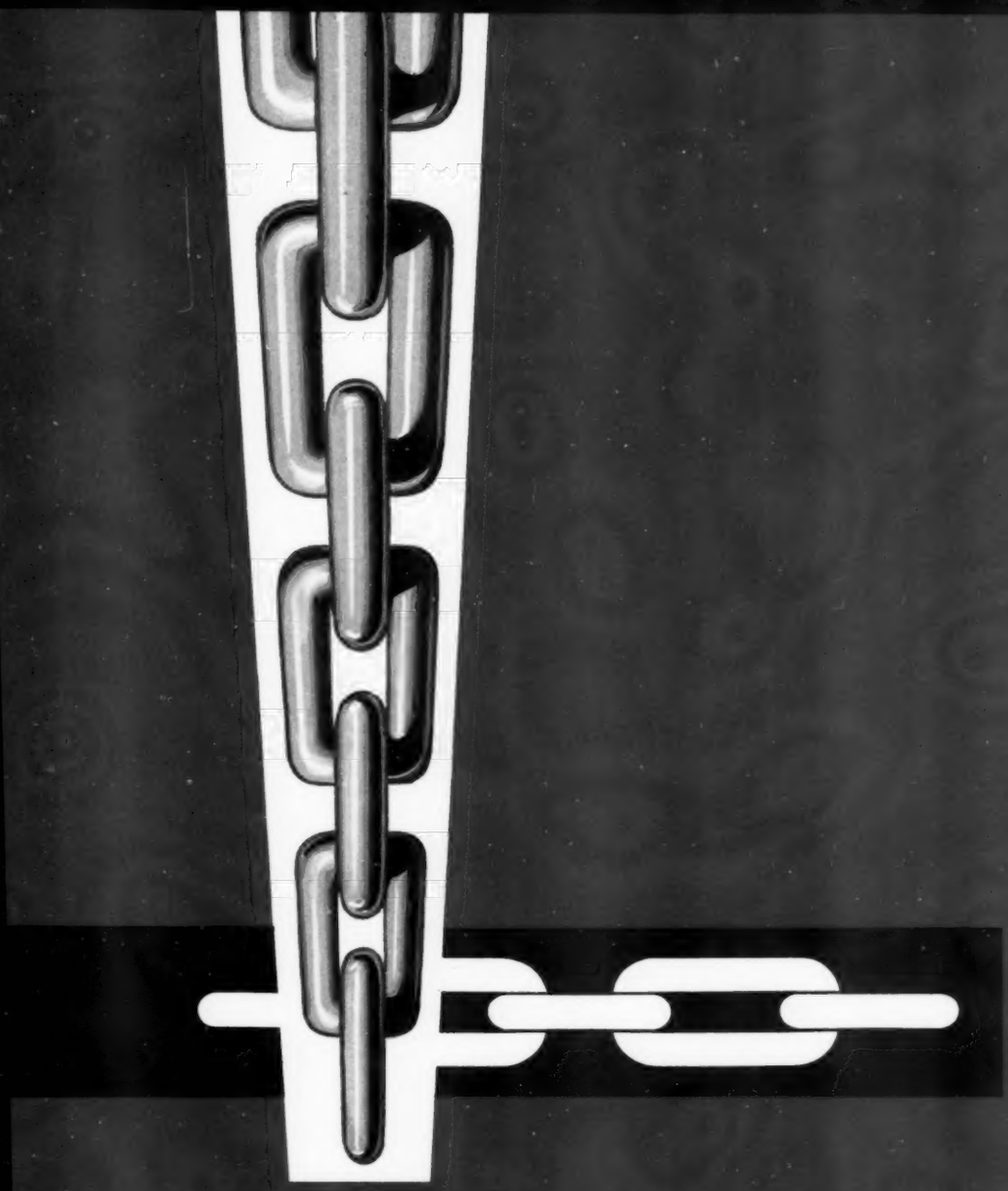

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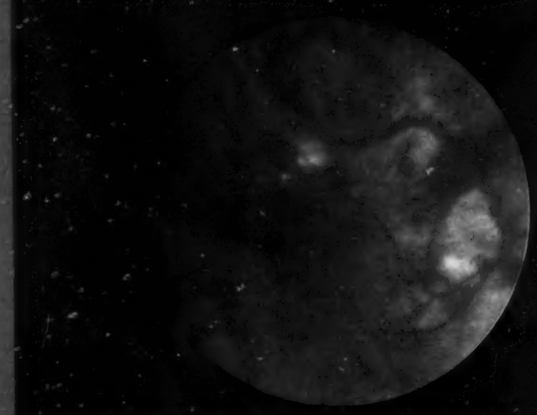
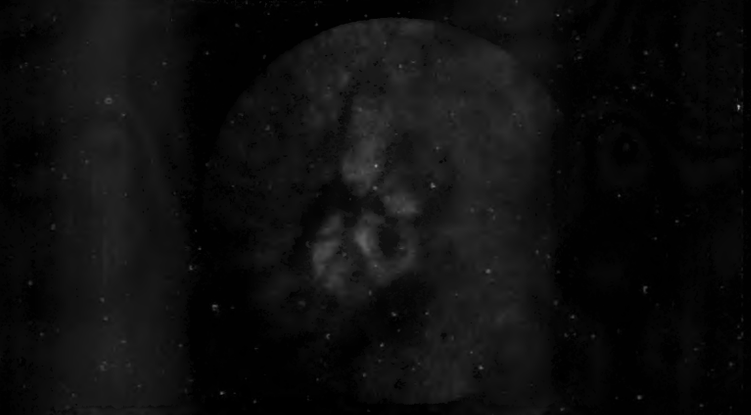


Anticipation of recurrent hemorrhage and visual defect is high in hypertensive patients.



After Adrenosem therapy. Note exudative areas. Maintenance therapy checks further hemorrhage.

Mastoidectomy with a bloody field obscures view, requires frequent suctioning.

After Adrenosem therapy. Note clearer operative field with minimized bleeding.

Multiple extraction without Adrenosem. Note seepage. Frequent suctioning is required.

After Adrenosem therapy. Note clearer field. Minimal bleeding facilitates surgery and promotes healing.

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Adrenosem is specific for conditions characterized by increased capillary permeability allowing oozing and seepage bleeding. To prevent seepage bleeding due to capillary permeability it is necessary to maintain tone of the capillary wall. This is supported by Pappenheimer's[1] work on capillaries. In cases of capillary permeability it is postulated that the connective material between the cells, which form the capillary wall, has lost its tone and allows the erythrocytes to pass through.

To confirm the action of Adrenosem in establishing capillary integrity the cheek pouch of a hamster was irritated with snake venom, which has the property of making the capillaries more permeable.[2] A great many petechiae appeared on the surface and a 500 X magnification showed the capillaries with extravasation of erythrocytes. Another animal was treated with Adrenosem, and 30 minutes later, the same amount of snake venom was used to irritate the cheek pouch. Microphotographs of the same 500 X magnification show the intact capillary walls and the actual blood cells coursing through the capillaries, without signs of escaping erythrocytes.

Fig. 1—*Trauma from snake venom produces hemoconcentration and stasis, indicative of altered vascular permeability.*

Fig. 2—*Trauma does not produce petechiae following Adrenosem injection.*

Fig. 1

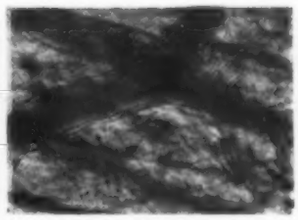

Fig. 2

Action

A systemic hemostat, Adrenosem restores capillary integrity by maintaining tone of intercellular tissue in the capillary wall. Adrenosem is unlike any hemostat available to medicine.[3,4] It does not interfere in any way with the blood clotting mechanism or its component parts. There is no sympathomimetic action and the blood pressure, cardiac rate and volume are not affected. Adrenosem may be administered simultaneously with any type of anesthetic, anticoagulant or vitamin K and heparin. Adrenosem will not interfere with the action of these agents.

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- postoperatively to prevent hemorrhage and check oozing: one to two ampuls (5 to 10 mg.) every two hours until there is no indication of undue bleeding. To maintain control, one ampul may be administered every three hours or 1 to 5 mg. orally t.i.d.
- to control active bleeding: one ampul (5 mg.) every two hours until bleeding is controlled; frequency of dose may then be diminished.
- to control mild, low-grade bleeding: one ampul (5 mg.) every three or four hours until bleeding is controlled; then 1 to 5 mg. orally four to five times daily until bleeding ceases.
- maintenance dosage to prevent bleeding in conditions where small vessel integrity may be impaired: 1 to 5 mg. orally t.i.d.; if bleeding ensues, dosage may be increased 1 to 5 mg. orally every three or four hours; if bleeding persists, oral dosage should be supplemented with one ampul (5 mg.) daily.
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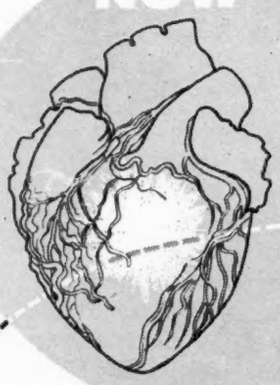

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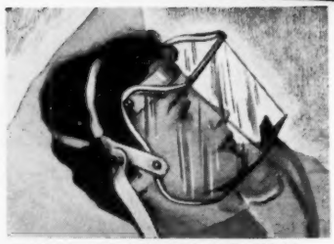

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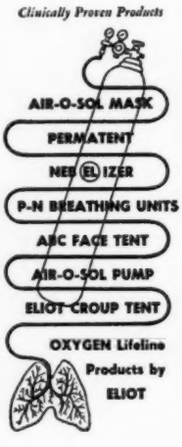

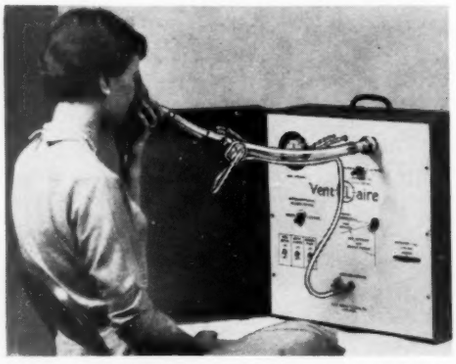

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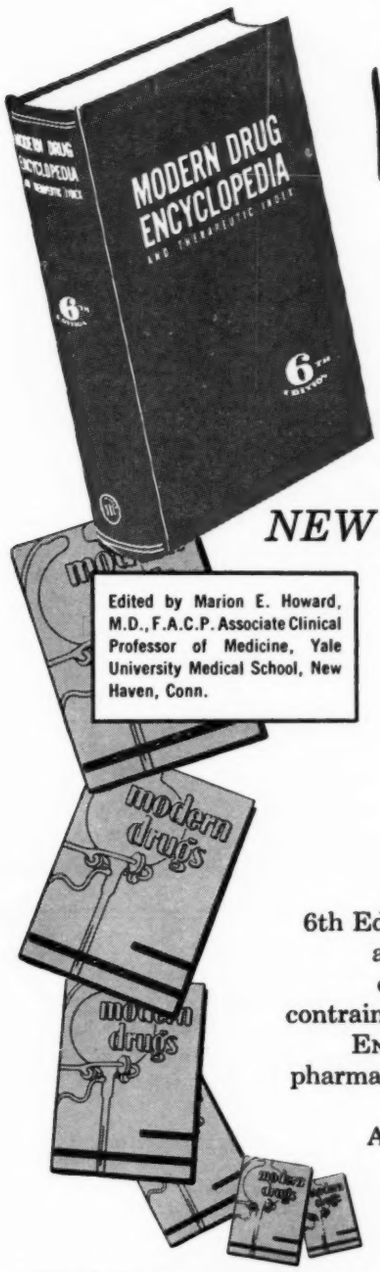

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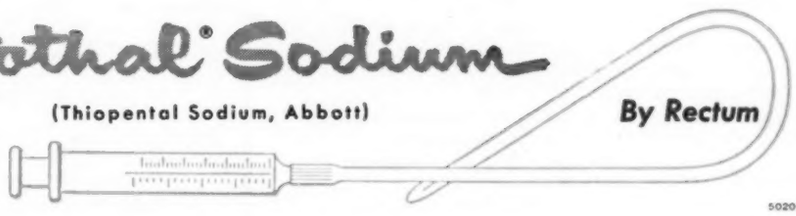

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An Announcement

The outstanding Symposium on BRONCHOPULMONARY DISEASES will be continued to completion in a special department in the following issues of The American Journal of Surgery—March, May, June, July, October and December.

The enthusiastic reception of the first section of the Symposium published in the January issue indicates an unusual interest in diseases of the lung.

Included in forthcoming issues are the following articles and authors:

Diagnosis and Treatment of Pulmonary Tuberculosis
Roger S. Mitchell, Trudeau, N. Y.

Current Status of Antimicrobial Agents in the Treatment of Pulmonary Tuberculosis
Nicholas D. D'Esopo, West Haven, Conn.

Pathology of Tuberculosis as Affected by Antibiotics
Oscar Auerbach, East Orange, N. J.

Mechanisms of Fatal Pulmonary Hemorrhage in Tuberculosis
J. Robert Thompson, Chicago, Ill.

Indications for Treatment of Tuberculosis in Children
Edith M. Lincoln, New York, N. Y.

The Role of Resection for Pulmonary Tuberculosis in Children and Adolescents
Morris Rubin, New York, N. Y.

Surgical Treatment of Pulmonary Tuberculosis
Norman J. Wilson, Orlando Armada, William B. O'Brien and William V. Vindzberg, Brookline, Mass.

Segmental Resection for Pulmonary Tuberculosis
J. Maxwell Chamberlain, New York, N. Y.

Home Management of Pulmonary Tuberculosis and Other Forms
Donald R. McKay, Buffalo, N. Y.

Present Status of Pneumotherapy in the Management of Pulmonary Tuberculosis
James H. Cullen, Albany, N. Y.

Management of Bronchiectasis in the Older Patient
Helen Sinclair Pittman, Boston, Mass.

Bronchiectasis
Francis M. Woods, Brookline, Mass.

Acute Lung Abscess
S. Aubrey Gittens and John P. Mihaly, New York, N. Y.

Lung Abscess—A Medico-Surgical Problem
David H. Waterman, Sheldon E. Domm and William K. Rogers, Knoxville, Tenn.

Airspace Abnormalities of the Lungs
Israel Rappaport and Edgar Mayer, New York, N. Y.

Roentgen Manifestations of Pulmonary Tension Disorders in Infants and Children
John A. Campbell, Indianapolis, Ind.

Cystic Disease of the Lung with Emphasis on Emphysematous Blebs and Bullae
Jerome R. Head, Chicago, Ill.

Pulmonary Air Cysts
David J. Dugan and Kenneth L. Hardy, Oakland, Calif.

Infected Cystic Disease of the Lung
Richard H. Meade, Grand Rapids, Mich.

Intralobar Bronchopulmonary Sequestrations
Andre J. Bruwer, Rochester, Minn.

Hydatid Cysts of the Lung
Louis R. Davidson, New York, N. Y.

Pulmonary Manifestations of Systemic Diseases
Eli H. Rubin, New York, N. Y.

Pulmonary Roentgenologic Changes in the Collagen Diseases
L. Henry Garland and M. A. Sisson San Francisco, Calif.

Generalized Amyloidosis
Irving J. Selikoff, Paterson, N. J.

Mycotic Infections of the Bronchial-Pulmonary Tract
Arthur Q. Penta, Schenectady, N. Y.

Pulmonary Histoplasmosis
Thomas F. Puckett, Denver, Colo.

Surgical Considerations in Pulmonary Coccidioidomycosis
Bert H. Cotton and J. W. Birsner, Los Angeles, Calif.

Silicosis and Asbestosis
O. A. Sander, Milwaukee, Wisc.

Beryllium Poisoning (Beryllosis)
H. E. Tebrock, New York, N. Y.

Pneumoconioses—Pathogenesis and Management
Arthur J. Vorwald, Detroit, Mich.

Foreign Bodies in the Bronchopulmonary Tract
Walter H. Maloney, Philadelphia, Pa.

Penetrating Wounds of the Lung
Aubre de L. Maynard, New York, N. Y.

Extrapleural Pulmonary Resection
Irving Sarot, New York, N. Y.

Present Concepts Relative to Autonomic Nerve Surgery in the Treatment of Pulmonary Disease
Osler A. Abbott, Emory University, Ga.

Thrombosis of Pulmonary Arteries
D. R. Keating, Cleveland, Ohio

Pulmonary Embolism and Infarction
Irving S. Wright and William T. Foley, New York, N. Y.

Fundamental Considerations in the Chemotherapy of Acute Pneumonias
Paul Bunn, Syracuse, N. Y.

Allergic Manifestations in the Respiratory Tract and Treatment
Joseph Harkavy, New York, N. Y.

Use of Corticotropin and Corticosteroids in Pulmonary Disease
M. S. Segal, J. A. Herschfus and A. Salomon, Boston, Mass.

Use of Exsufflation with Negative Pressure in Postoperative Patients
Edward K. Williams and Duncan A. Holaday, New York, N. Y.

Indications for Tracheotomy Following Thoracic Injuries or Operations
Mark H. Williams, Binghamton, N. Y.

Management of Impaired Respiratory Function
James L. Whittenberger, Boston, Mass.

Effect of Pulmonary Disease in Inhalation Anesthesia
Joseph Giuffrida and Dante Buzzari, Brooklyn, N. Y.

Importance of Rehabilitation in Thoracic Surgery
Albert Haas and Howard A. Rusk, New York, N. Y.

Selection and Management of Patients with Thoracic Diseases for Air Travel
Burgess L. Gordon, Philadelphia, Pa.

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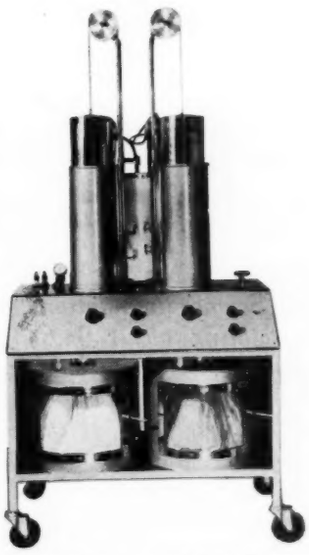

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NOTES AND QUOTES

EARL C. MECHTENSIMER has been selected as the 1954 recipient of the Fred Geck Award. This award has been established by Davis & Geck, Inc., in memory of Fred Geck who was one of the two founders of the organization which manufactures surgical sutures and specialties.

The Fred Geck Award will be presented annually to the member of the senior class in Hospital Administration at Northwestern University whose graduate study project shows the most thorough research on a subject of high current interest to hospitals. A cash prize of $100 will go to the author and an additional $150 will be used to defray the expense of publishing the paper in a medical journal.

Mr. Mechtensimer's article on "Organization and Management of a Radioactive Isotope Laboratory in a General Hospital" was published in the September, 1954 issue of Hospital Administration Review.

The familiar "many tailed" bandage has been used for centuries to hold the sterile gauze pad in place after surgery. Something new has been introduced in the patented Muller Surgical Binder. It is a shaped, single-sheet, washable binder to be worn over the pad and has a self-locking buckle that insures comfort. It is loosened or tightened by web strips—each strip closed with its own buckle. It does away with adhesive tape next to the body, a boon to patients, nurses and doctors. For reuse the buckles slide off for easy laundering. Sold through surgical supply houses.

SOME forms of heart disease and cancer, as well as diabetes and mental disease, have a tendency to run in families, according to the statisticians of the Metropolitan Life Insurance Company. New evidence of such a tendency has recently become available from a study of the mortality experience of a large number of life insurance companies from 1935 to 1950.

Mortality among these policyholders who had two or more close relatives with heart disease acquired before age sixty was about 40 per cent higher than that for standard risks, and most of the excess mortality was attributable to the high death rate from diseases of the heart and vascular system.

For those with a family history of heart disease who were also slightly overweight or had a slight blood pressure elevation, the mortality was about 70 per cent higher than the average, whereas among those free of the overweight or blood pressure impairment, the mortality was nearly 25 per cent above the average, according to the experience of two companies.

Among policyholders reporting two or more cases of cancer in parents or other members of the family under age sixty, mortality from cancer was more than twice the average. Policyholders with even a single diabetic at any age in the family experienced a mortality from diabetes nearly twice the average.

The study also showed that mortality among the insured persons who reported two or more cases of mental disease in the family before age sixty was slightly above average for all causes combined, and was several times the normal for suicide, a fairly reliable index of mental disorder.

Other studies also provide evidence that persons with a good family history of longevity live longer, on the average, than those with a poor record of parental longevity.

"While the effect of family history on longevity is appreciable," the statisticians observe, "it is nevertheless small compared with the gains in longevity observed through the improvement in environment since the turn of the century."

The National Science Foundation has announced 216 grants totaling about $2,650,000 for the support of basic research in the natural sciences, for conferences and studies on science, scientific information exchange, for scientific manpower and for travel of American scientists to international scientific meetings. This is the first group of awards to be made during fiscal year 1955 by the Foundation for the support of basic research and related matters. Since the beginning of the program in 1951, over 1,100 such awards have been made, totaling about $11,141,000. In addition, the first grant, totaling $100,000, was made under a special appropriation for the International Geophysical Year.

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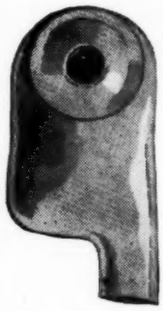
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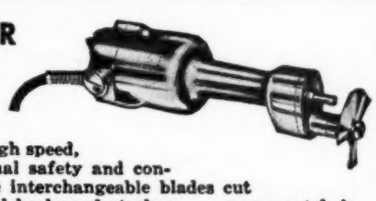
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Tuberculosis is a "catching" disease. It is spread by people with active, or open, tuberculosis who cough up germs. Approximately 110,000 persons in this country are falling victim to the disease each year—one person every five minutes. Approximately 20,000 are dying of tuberculosis annually—one every twenty-two minutes. Time was when the number of people ill with tuberculosis was incalculable and the toll of lives was around 150,000 a year.

Fifty years ago the fact that TB was a "catching" disease was little recognized. People were inclined to put it in the category with death and taxes, as belonging to the inevitable; certainly as leading more or less swiftly, but always directly, to death.

Today we know that death from tuberculosis is not inevitable, that tuberculosis can be cured. We also know that it can be prevented. Remarkable strides have been made against this infectious disease since 1904 when the National Tuberculosis Association was founded and, coordinating various efforts throughout the country, spearheaded a nationwide attack against the No. 1 cause of death of the day.

The campaign against tuberculosis has borne fruit. The death rate from the disease has been forced down approximately 90 per cent in fifty years.

Yet, with all the progress made, tuberculosis is today the gravest public health problem in the United States, the most serious infectious disease problem in the world. The NTA and its affiliates are deeply conscious of these facts as they observe the fiftieth birthday of the NTA.

A TOTAL of over 3,100 registrants from fifty nations attended the Second World Congress of Cardiology which was combined with the Twenty-Seventh Scientific Sessions of the American Heart Association at the National Guard Armory in Washington, D. C., in September. About one-third were physicians from abroad.

Dr. Paul D. White of Boston, who served as President of the Congress, was elected President of the International Society of Cardiology which sponsors these Congresses. He succeeded Dr. Charles Laubry of Paris, who has held the post for the past four years and who presided over the first international cardiology congress in Paris in 1950. Other officers named at a meeting of the Society's Council include: First Vice President, Prof. Ignacio Chavez, Mexico City; Second Vice President, Prof. D. E. Bedford, London; Secretary-General, Prof. Pierre Duchosal, Geneva; Treasurer, Dr. Louis N. Katz, Chicago; Assistant Secretary, Dr. John Palmer, Montreal.

The Third World Congress of Cardiology will be held in Brussels, Belgium in 1958. The Inter-European Congress of Cardiology will be held in Stockholm in 1956, and the Inter-American Congress of Cardiology will convene in Havana in the same year.

New plants for the manufacture of terramycin® and other Pfizer antibiotics, pharmaceuticals and chemicals will soon be constructed in Chile and Argentina, as announced by John E. McKeen, President of Chas. Pfizer & Co. of Brooklyn, N. Y. Mr. McKeen recently returned from a South American tour that took him to Peru, Chile, Argentina, Ecuador and Colombia. In Chile Mr. McKeen was notified by President Carlos Ibanez that he had been awarded the Order of Merit of Bernardo O'Higgins, highest that Chile confers on non-nationals.

AN entirely new corticosteroid, fluorohydrocortisone acetate, which is ten times as potent topically as hydrocortisone, is being made available by the E. R. Squibb & Sons Division of Olin Mathieson Chemical Corporation under the name florinef. The new drug was developed in the laboratories of the Squibb Institute for Medical Research, New Brunswick, N. J. It is being marketed initially in lotion and ointment forms.

A scholarship in anesthesiology has been established at The New England Hospital, Boston, Massachusetts, the department of which is approved for the required two-year residency training. The scholarship of $2,500 a year, including full maintenance, will be awarded annually to a women with a degree of Doctor of Medicine from an approved medical school and with a one-year approved internship. Both

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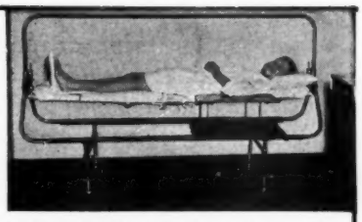

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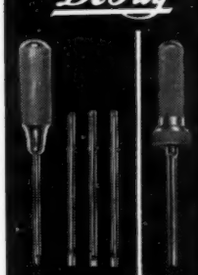

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APPOINTMENT of Dr. Harriet A. Geer as senior research chemist for Parke, Davis & Company has been announced by Dr. Leon A. Sweet, Vice President and Director of research and products development. Dr. Sweet said Dr. Geer would become head of the central records office, which serves as the nerve center for all research department activity and is a clearing house for chemical and biologic information.

"A principal function of this office," Dr. Sweet pointed out, "is an attempt to relate chemical structure with biological activity."

Dr. Geer, the third woman PH.D. to be named to the Parke-Davis staff, was graduated from Smith College in 1930 with a B.A. degree in chemistry. She obtained her M.A. in 1932 and PH.D. in 1935, both from the University of Kansas. Her graduate work was done in the field of chemistry. Following her doctorate work she had nine years of laboratory experience, first with the chemical research laboratory at Yale University Medical School and later with the virus chemotherapy division of the Michigan State Health Laboratory. From 1946 to 1954, Dr. Geer was with the Chemical Biological Coordination Center of the National Research Council at Washington, D. C. Immediately prior to joining Parke-Davis, she was head of the chemical section of the Center.

Is exogamous artificial insemination a benefit to humanity or should it be considered a crime? Its future hangs on legislation. The decision may well depend on what legislators believe the voters want rather than on what might be best for them. It is an important problem and one requiring thoughtful study, according to Wendy Stewart, LL.B., M.D., in her article, "What Should the Doctor Know About Exogamous Artificial Insemination?" which appeared in the November, 1954 Journal of the American Medical Women's Association.

Some people think artificial insemination so beneficial that it should be encouraged; that the child living in a home where he was so much desired and whose characteristics have been selected, has an unusually good chance of sound development. Others consider the practice a criminal offense, and that the donor must be so depraved that he could contribute only poor hereditary characteristics.

"There are serious aspects of social, moral and legal welfare to be considered . . . as things stand at present there is much risk of an outcome detrimental to the hoped-for child. At best . . . there is doubt as to his legal status; at worst . . . he is regarded as an illegitimate child." Instead of forcing legislation prematurely it would be better, Dr. Stewart believes, to eventually translate existing custom into law. This can come if the practice is demonstrably widespread, with safeguards protecting all concerned.

A canon of professional ethics should include contracts protecting the child, the mother, her husband, the donor and the physician. A survey would show what had become custom and what practices are most effective. Legislation should include surveys of existing laws and the drafting of model laws establishing the legality of the practice and the legitimacy of the children, these laws to be put into effect state by state.

Most of these problems can now be resolved if the child is adopted legally by the married couple. Such a procedure is confidential; the stepfather cannot, for example, defend himself for failure to provide for the child on the grounds of non-paternity; and all parties are given the rights of legitimacy.

"While the ultimate goal should be legislation . . . the immediate one should be adoption."

DR. RUSSEL L. CECIL of New York City, nationally known internist, medical teacher and medical editor, has been honored as recipient of the 1954 Honor Award given by the American Medical Writers' Association. Dr. Cecil is Emeritus Professor of Medicine at Cornell University and editor of "A Textbook of Medicine." The Honor Award is given from time to time "to a non-member of the Association who has made distinguished contributions to medical literature."

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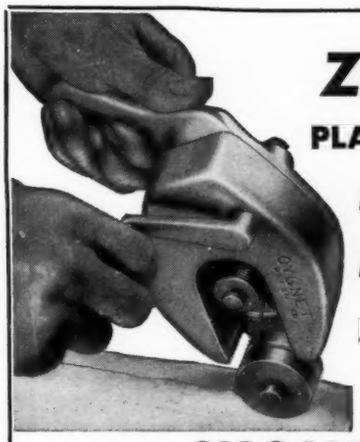

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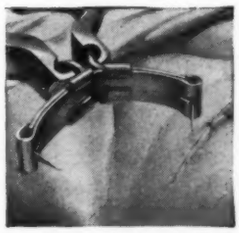

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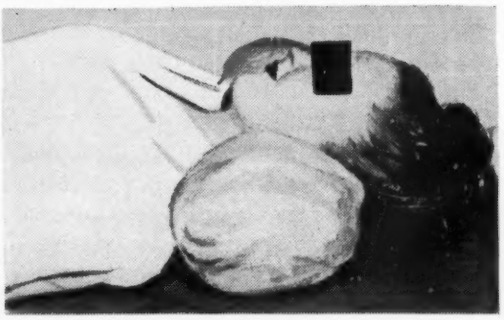

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NOTES AND QUOTES

Dr. Richard M. Hewitt of Rochester, Minnesota, nationally known medical writer and editor, has been honored as recipient of the 1954 Distinguished Service Award given by the American Medical Writers' Association. Dr. Hewitt is the Senior Consultant, Section on Publications, Mayo Clinic; Assistant Professor of Medical Literature, Mayo Foundation, University of Minnesota; former Assistant Editor, *J. A. M. A.* Dr. Hewitt has served as Chairman of the Educational Committee of the American Medical Writers' Association since it was organized in 1951 and is largely responsible for the establishment of the new four-year courses in medical journalism and writing at the University of Illinois and the University of Missouri. The Distinguished Service Award is given annually to a member of the Association, "who has made distinguished contributions to medical literature or rendered unusual and distinguished service to the medical profession."

The Cardiac Pacemaker, developed by Dr. P. M. Zoll, provides external electric stimulation to the heart in cardiac asystole due to anesthesia, Stokes-Adams disease, or any cause. The success of the Cardiac Pacemaker in resuscitating the failing heart has proved the efficacy of this life-saving instrument. It was designed to meet emergency situations. It is the only proven externally applied instrument of its type and is very simple in its application. Flat disk type electrodes, which do not penetrate the skin, are applied to the intact chest. The Cardiac Pacemaker then automatically provides an electric stimulus to which the heart responds with a ventricular contraction. This response can maintain consciousness, pulse beat and blood pressure until spontaneous cardiac activity returns.

FROM The World Health Organization we learn that in the fight against syphilis, penicillin is considered as a fully effective, non-toxic and relatively inexpensive remedy. A single injection will cure a patient suffering from early syphilis in from ten to fifteen days at a cost of between 93 cents and $1.40.

A study carried out by WHO in fifty-five countries reveals the extent to which penicillin alone is now used, most countries having discontinued metal chemotherapy (bismuth, arsenic and mercury) which was the method used prior to penicillin treatment. Metal chemotherapy is, however, still used in some countries for treatment consolidation purposes.

The World Health Organization has taken the opportunity offered by the tenth anniversary of the advent of penicillin therapy and the centenary of Paul Ehrlich, discoverer of chemotherapy, to review the development of syphilis treatment methods. A recent issue of the *Bulletin of the World Health Organization* is devoted exclusively to the study of this question.

Although syphilis has become much less serious in some countries in the last decade, it continues to be an important public health problem in many others and from the international point of view. WHO, in fact, estimates that there are about twenty million syphilitics in the world today and that in some special areas in certain countries up to 80 per cent of the population may be affected.

The existence of these reservoirs of infection (according to WHO more prevalent in ports than in inland cities, both in developed and underdeveloped areas) constitutes a public health danger at a time when rapid transport by land, sea and air is now available, when desert treks and migrations have increased considerably in volume, and when commercial intercourse between countries is accelerating.

The copper pill rolling pan used in the middle of the last century by William R. Warner, Philadelphia druggist, to manufacture America's first mass-produced, sugar-coated pill was presented today to the Smithsonian Institute to become part of an exhibit of early American pharmaceutical manufacturing equipment.

The French had begun to sugar-coat bitter pills in the 1830's. Mr. Warner introduced the process of mass production to the United States in 1856. His coated pills became so popular with long-suffering patients that soon he branched into wholesale manufacturing. Mr. Warner's equipment, which included a copper pitcher used for pouring the sugar syrup, was donated to the Smithsonian Institution by Warner-Chilcott Laboratories, the pharmaceutical division of Warner-Hudnet, Inc.

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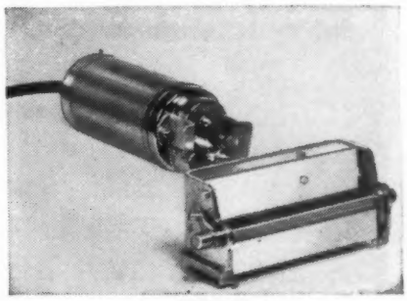

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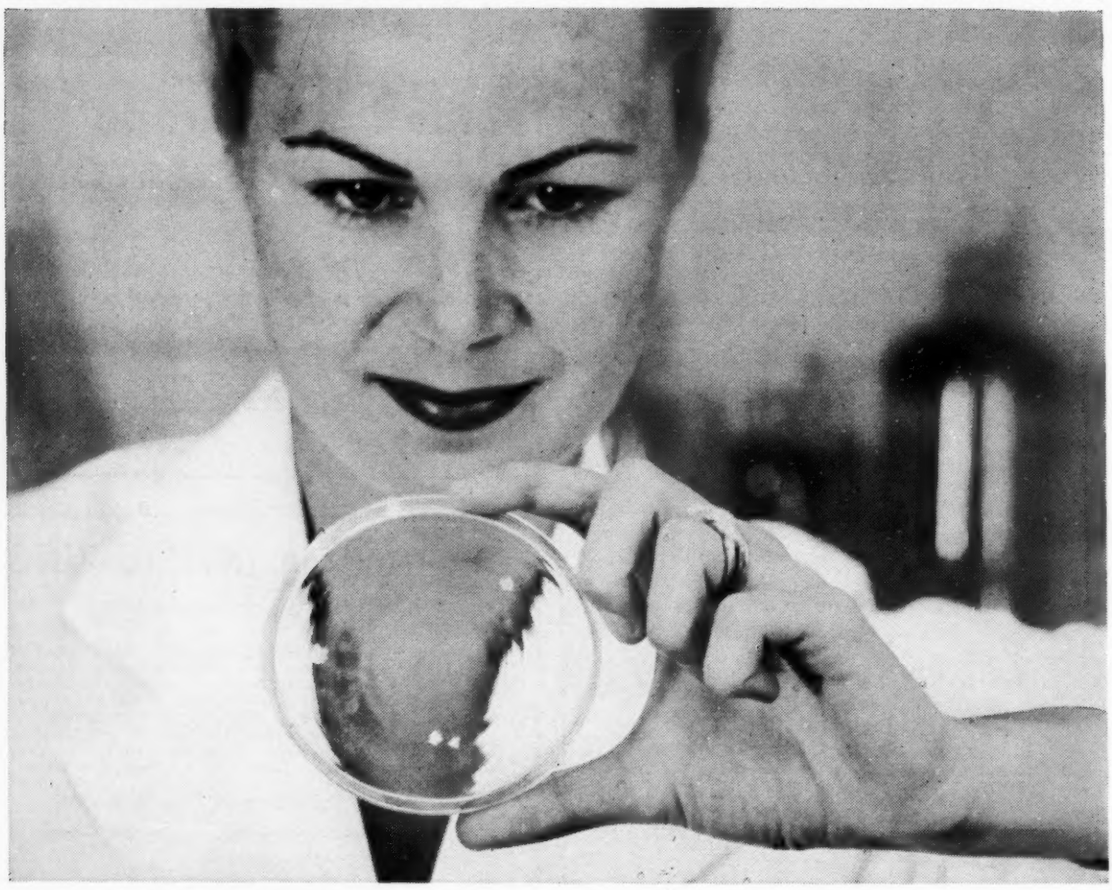

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References: 1. N.N.R. 1954, p. 107. 2. Poth, E. J., J.A.M.A. *153*:1516, December 26, 1953.

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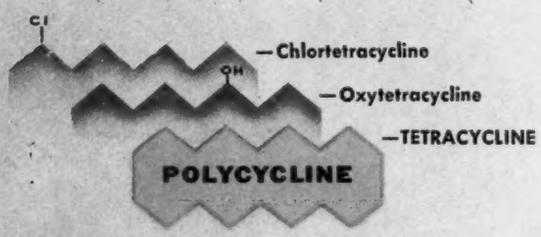

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